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REVIEW

Characters, functions and clinical perspectives of long non-coding RNAs

Ruifang Wu[1] · Yuwen Su[1] · Haijing Wu[1] · Yong Dai[2] · Ming Zhao[1] · Qianjin Lu[1]

Abstract It is well established that most of the human genome and those of other mammals and plants are transcribed into RNA without protein-coding capacity, which we define as non-coding RNA. From siRNA to microRNA, whose functions and features have been well characterized, non-coding RNAs have been a popular topic in life science research over the last decade. Long non-coding RNAs (lncRNAs), however, as a novel class of transcripts, are distinguished from these other small RNAs. Recent studies have revealed a diverse population of lncRNAs with different sizes and functions across different species. These populations are expressed dynamically and act as important regulators in a variety of biological processes, especially in gene expression. Nevertheless, the functions and mechanisms of most lncRNAs remain unclear. In this review, we present recent progress in the identification of lncRNAs, their functions and molecular mechanisms, their roles in human diseases, their potential diagnostic and therapeutic applications as well as newer technologies for identifying deregulated lncRNAs in disease tissues.

✉ Ming Zhao
  zhaoming307@csu.edu.cn

✉ Qianjin Lu
  qianlu5860@gmail.com

[1] Hunan Key Laboratory of Medical Epigenomics,
  Department of Dermatology, The Second Xiangya Hospital,
  Central South University, #139 Renmin Middle Road,
  Changsha 410011, Hunan, China

[2] Clinical Medical Research Center, The Second Clinical
  Medical College of Jinan University (Shenzhen People's
  Hospital), Shenzhen 518020, Guangdong, China

Introduction

With the development of next generation sequencing methods and DNA tiling arrays, it has become possible to sequence the complete human transcriptome. Numerous studies have revealed that the human genome consisted of 20,500 of coded genes, which is only less than 2 % of the genome (Archer et al. 2015). Not surprisingly, at least 90 % of the genome is actively transcribed into non-coding RNAs (ncRNAs), which have no protein coding potentiality (Birney et al. 2007). ncRNAs can be approximately classified into two groups: (1) classical 'housekeeping' RNAs, such as rRNAs, tRNAs, small nuclear RNAs (snRNAs) and small nucleolar RNAs (snoRNAs), which are constitutively expressed and play critical roles in protein biosynthesis; and (2) 'regulatory' RNAs that include small regulatory RNAs (*e.g.*, microRNAs, siRNAs and piRNAs) and long non-coding RNAs (lncRNAs). The functions of most small RNAs have been clarified, however, our understanding of lncRNAs is still obscure.

LncRNAs are defined as all transcripts that are greater than 200 nucleotides in length but lack of protein-coding capacity (Iyer et al. 2015). LncRNAs are mainly transcribed by RNA polymerases (RNAP) II or III in mammal animals, and additionally, by RNAP IV and V in plants (Struhl 2007; Bierhoff et al. 2010). Due to the wide applications of high throughput RNA-sequencing (RNA-seq) approaches, thousands of lncRNAs in many organisms, such as mammal animals and plants, have been identified. For instance, about 6480 lncRNAs were identified from 200 *Arabidopsis thaliana* transcriptomic data sets, with either organ-specific

or stress-induced expression profiles (Liu et al. 2012). Nearly 50,000 annotated lncRNA genes have been discovered in the human genome (Iyer et al. 2015). LncRNAs are processed by splicing or non-splicing, polyadenylation or non-polyadenylation, and can be located in the nucleus or cytoplasm (Wierzbicki 2012), which play *cis-* or *trans*-regulators of gene transcription, and are involved in a wide range of biological processes. This review summarizes recent progress in the research of lncRNAs, with an emphasizing on their role in gene expression regulation and human diseases.

Classification of lncRNAs

According to the current literature, there are several different classification methods. LncRNAs can be categorized as sense, antisense, intronic, intergenic and bidirectional lncRNAs based on their genomic proximity to protein coding genes (Ponting et al. 2009; Rinn and Chang 2012). Another classification includes "high abundance" and "low abundance" lncRNAs. Some publications have divided lncRNAs into *cis-* and *trans*-acting lncRNAs by function (Wang et al. 2011b). Recently, Di Gesualdo et al. (2014) provided an updated classification of lncRNAs: (1) lncRNAs that are transcribed from *loci* distinct from sense transcript-encoding gene *loci* are termed long intergenic non-coding RNAs (lincRNAs); (2) exceptionally long lncRNAs are termed macroRNAs and very long intergenic non-coding RNAs (vlincRNAs); (3) lncRNAs that are bidirectionally transcribed from the enhancer and promoter regions are referred to as enhancer-associated RNAs (eRNAs) and promoter-associated long RNAs (PALRs), respectively; (4) transcripts on the antisense strand can generate natural antisense transcripts (NATs) with varying degrees of overlap, including divergent and convergent NATs.

Functions of lncRNAs

Due to their low sequence conservation between species, lncRNAs were initially thought to be non-functional and even spurious transcriptional noise arising from low RNA polymerase fidelity (Struhl 2007; Bierhoff et al. 2010). In recent years, some functions of lncRNAs have been found, including participating in the formation of RNA–protein complexes or subcellular structures as scaffolds, modulating protein activity and localization by binding with specific proteins, regulating gene expression and controlling genomic imprinting and X-inactivation (Clemson et al. 2009; Kornienko et al. 2013).

lncRNAs act as scaffolds

The formation of diverse RNA–protein complexes or subcellular structures is the common function of many lncRNAs, and it is within these structures where lncRNAs carry out scaffolding functions (shown in Fig. 1a). The earliest evidence of this phenomenon came from the discovery of telomerase (Greider and Blackburn 1985).

Telomerase is a ribonucleoprotein enzyme that is able to add telomere repeats to the end of the chromosomes
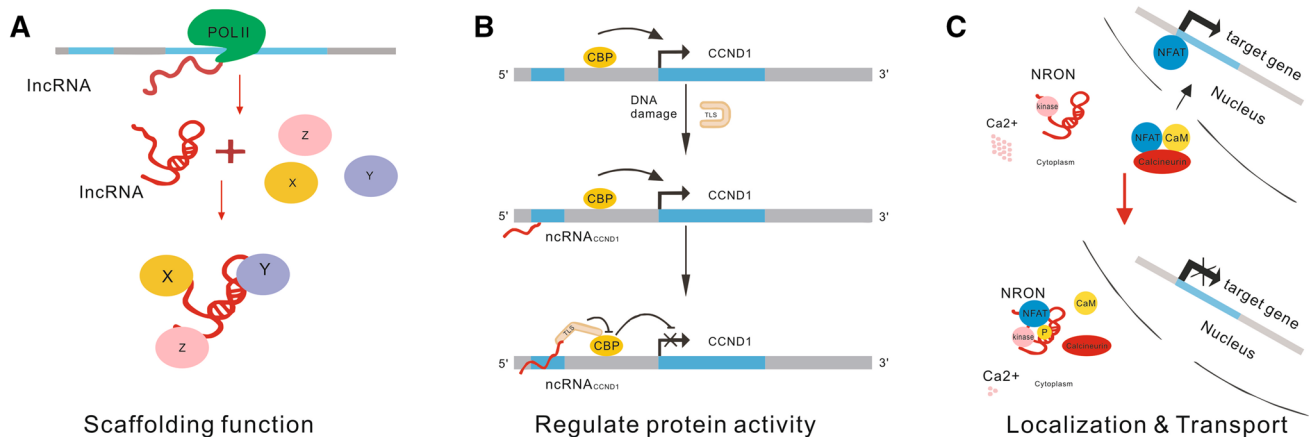

Fig. 1 LncRNAs interact with proteins to function as scaffolds, influence protein activity and modulate protein localization. **a** LncRNAs can participate in the formation of diverse RNA–protein complexes or subcellular structures, where they carry out scaffolding functions. **b** LncRNAs can be involved in modulating the activity of proteins. $ncRNA_{CCND1}$ is induced upon DNA damage and enhances both the cleavage of TLS as well as its inhibition of CBP functions, thereby repressing CCND1 transcription. **c** LncRNAs can influence protein localization: lncRNA NRON binds to the transcription factor NFAT and limits the nuclear-cytoplasmic trafficking of NFAT, ultimate leading to the repression of NFAT target gene expression. POL II, RNA polymerase II; Ca^{2+}, Calcium ion; CaM, calmodulin; Calcineurin, Ca^{2+}/calmodulin-dependent phosphatase calcineurin

and which is expressed in most malignant tumor cells. The telomerase holoenzyme consists of a protein component, a reverse transcriptase termed telomerase reverse transcriptase (TERT) and an RNA primer, also known as telomerase RNA component (TERC) (Feng et al. 1995). TERC act as a template for TERT-catalyzed reverse transcription and as a molecular scaffold for the polymerase enzyme around the RNA (Lingner et al. 1997).

Another example of lncRNA scaffolding is the study of the composition of paraspeckles. Paraspeckles are a relatively new class of subnuclear bodies found in the interchromatin space of mammalian cells. These bodies are critical for the control of gene expression through the nuclear retention of RNA that contains double-stranded regions that have been subject to adenosine-to-inosine editing (A–I editing) (Fox and Lamond 2010). Clemson et al. (2009) have found that the nuclear enriched autosomal transcript 1 (NEAT1) RNA is associated with intense concentrations of PSP1 and P54, which demark paraspeckles in vivo and in vitro (Fox et al. 2002). These authors also proved that paraspeckles may initially form when NEAT1 RNA is transcribed and that their spread throughout the nucleus corresponds with the spread of NEAT1 RNA. Furthermore, an increase in NEAT1 expression causes a parallel increase in paraspeckle number, and knockdown of NEAT1 RNA leads to loss of paraspeckles (Clemson et al. 2009; Fox and Lamond 2010). Taken these results together, it is clear that NEAT1 is essential to the formation of paraspeckles and may function as, but is not necessarily limited to, a scaffold.

lncRNAs modulate protein activity and localization

Evidence is accumulating that lncRNAs, aside from their scaffolding function, are also involved in modulating the activity and localization of protein complexes. Wang et al. (2008) identified a series of single-stranded ncRNA transcripts with low copy number (known as ncRNA$_{CCND1}$) that are induced in response to DNA damage signals and tethered to the 5' regulatory regions of the cyclin D1 (*CCND1*) gene. These authors found that ncRNA$_{CCND1}$ serves as a molecular "ligand" for translocation in liposarcoma (TLS), an RNA-binding protein that represses *CCND1*. ncRNA$_{CCND1}$ interacts with the C-terminus of TLS to enhance the binding and cleavage of TLS to CREB-binding protein (CBP), which can inhibit histone acetylation of the *CCND1* promoter and repress its expression (Wang et al. 2008; Guttman and Rinn 2012) (shown in Fig. 1b).

Similarly, the lncRNA non-coding repressor of NFAT (NRON) was found to repress nuclear factor of activated T cells (NFAT), a Ca^{2+}-regulated transcription factor that controls gene expression in many cell types (Sharma et al. 2011) (shown in Fig. 1c). The activation of NFAT

protein is regulated by the phosphorylation status of the NFAT regulatory domain, which is necessary and sufficient for nuclear transport (Sharma et al. 2011). Phosphorylated NFAT proteins reside in the cytoplasm of resting cells, and dephosphorylated NFAT protein translocates to the nucleus to activate target gene expression when cells are stimulated by an increase in the intracellular Ca^{2+} concentration (Sharma et al. 2011). The lincRNA NRON can bind to NFAT proteins together with NFAT kinases and is involved in the maintenance of phosphorylated NFAT proteins (Sharma et al. 2011; Guttman and Rinn 2012). Consequently, the lncRNA NRON renders NFAT proteins inactive and inhibits their trafficking from cytoplasm to nucleus, ultimately leading to inhibition of NFAT target gene expression (Sharma et al. 2011; Guttman and Rinn 2012).

lncRNAs regulate gene expression

The most important function of lncRNAs is their role in regulating gene expression (Gutschner and Diederichs 2012; Ma et al. 2012). This function was confirmed first by loss-of-function studies on most intergenic lncRNAs (lincRNAs) expressed in mouse embryonic stem (ES) cells. This analysis revealed that knockdown of lncRNAs has significant consequences on gene expression patterns (Guttman et al. 2011). As we will show, lncRNAs have been demonstrated to regulate protein-coding gene expression through a variety of mechanisms, including epigenetic modifications, transcription and post-transcriptional processing (Mercer et al. 2009; Kornienko et al. 2013).

Epigenetic modification-dependent pre-transcriptional regulation

Studies from several research groups have shown that lncRNAs are involved in epigenetic regulations by recruiting chromatin-remodeling complexes, such as PRC1, PRC2, MLL and G9A, to specific locations in the genome (Nagano et al. 2008; Pontier and Gribnau 2011; Wang et al. 2011a) (shown in Fig. 2a).

HOTTIP lncRNA is expressed in the *HOXA* cluster, whose higher-order structure is dependent on positional identity (Wang et al. 2011a; Kornienko et al. 2013). Wang et al. (2011a) have demonstrated a looped conformation within the 5' *HOXA* locus and a linear conformation within the 3' *HOXA* locus in anatomically distal cells, which is diametrically opposite to the pattern in anatomically proximal cells. Their research showed that chromosomal looping brings the *HOTTIP* gene into close proximity to the 5' *HOXA* genes. Then, the *HOTTIP* gene produces HOTTIP lncRNA, which directly binds the adaptor protein WDR5 and targets the WDR5/MLL histone-modifying complexes
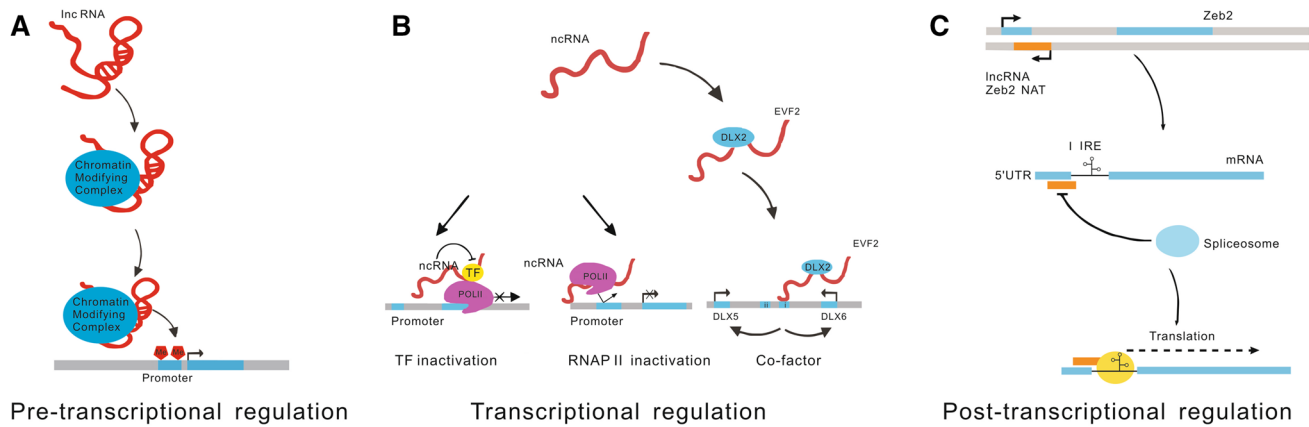
Fig. 2 LncRNAs regulate gene expression by multiple mechanisms. **a** LncRNAs can recruit chromatin-modifying complexes to specific genomic loci to regulate target gene expression. **b** LncRNAs influence the general output of mRNAs by directly affecting the loading and activity of RNAPII (*middle panel*) or general transcription factors (*left panel*). In addition, lncRNAs can act as co-factors or inhibitors to regulate the activity of a particular transcription factor (*right panel*). The *right panel* shows that the lncRNA Evf2 acts as a co-acti-vator of the transcription factor DLX2 to regulate *DLX5* and *DLX6* gene transcription. **c** Antisense lncRNAs can mediate the alternative splicing of mRNA by forming RNA duplexes. LncRNA Zeb2 NAT can overlap the 5′splice site in an intron located in the 5′-untranslated region (UTR) of Zeb2 mRNA and prevent the splicing of the intron, causing an up-regulation of Zeb2 protein without significantly altering the level of Zeb2 mRNA

to the 5′ *HOXA* locus, driving histone H3 lysine 4 trimethylation and transcription activation.

Except for HOTTIP,which acts in *cis*-regulation, there are many other lncRNAs regulated gene expression in *trans*, such as HOTAIR (Rinn et al. 2007). HOTAIR is transcribed from the *HOXC* locus and represses transcription in *trans* across 40 kb of the *HOXD* cluster by recruiting the PRC2 complexes (Rinn et al. 2007). The epigenetic regulatory-mechanism mediated by lncRNA may explain the question of how chromatin-remodeling complexes gain locus specificity (Mercer et al. 2009; Kornienko et al. 2013).

Recent evidence rasied the possibility that lncRNAs may interact with target genes through formation of RNA–DNA triplex structures, serving as a link between chromatin and chromatin modifiers. Very recently, Mondal et al. (2015) have demonstrated that lncRNA MEG3 regulates the TGF-β pathway genes through RNA–DNA triplex formation. Genome-wide mapping of MEG3 binding sites reveals that MEG3 modulates the activity of TGF-β pathway genes by binding to distal regulatory elements containing GA-rich sequences, which guide MEG3 to the chromatin through RNA–DNA triplex formation, and then contributing to PCR2 recruitment. O'Leary et al. (2015) named a new lncRNA PARTICLE (gene *PARTICLE*, promoter of *MAT2A*-antisense radiation-induced circulating lncRNA), which can forms a DNA-lncRNA triplex upstream of a *MAT2A* promoter CpG island and interacts with the transcription-repressive complex proteins G9a and SUZ12 (subunit of PRC2) to repress *MAT2A* via methylation (Yang et al. 2001). These findings implicate lncRNA play as a recruitment platform for gene-silencing machineries by RNA–DNA triplex formation.

Transcriptional regulation

As the first critical step in gene expression, the transcription of protein-coding genes into mRNA is an intricate biological process that consists of multiple steps, from the formation of the preinitiation complex to transcript elongation (Espinoza et al. 2004; Yakovchuk et al. 2009). Each step in the transcription reaction has the potential to be regulated by *trans*-acting activators and repressors (Espinoza et al. 2004; Mariner et al. 2008; Yakovchuk et al. 2009, 2011). It is presently becoming clear that ncRNAs also play key roles in regulating the process of transcription. Diverse lncRNAs have been identified as regulators of nearly every step in the process of transcription and act through different mechanisms (Yakovchuk et al. 2009).

In eukaryotes, RNAP II transcribes protein-coding genes into mRNA in collaboration with general transcription factors (Espinoza et al. 2004; Mariner et al. 2008; Yakovchuk et al. 2009, 2011). Some lncRNAs have been reported to influence the general output of mRNAs by directly affecting the loading and activity of RNAP II or general transcription factors (shown in Fig. 2b). As an example, Alu RNA in human (Mariner et al. 2008; Yakovchuk et al. 2009) and B2 RNA in mouse (Espinoza et al. 2004; Yakovchuk et al. 2009) have been shown to function as general repressors of mRNA transcription and are transcribed by RNAP III from short interspersed elements (SINEs) (Yakovchuk et al. 2009). The levels of Alu and B2 RNA

increase in response to heat shock, at which point they bind directly to RNAP II to assemble into preinitiation complexes at the promoter. This interaction disrupts important contacts between RNAP II and the promoter DNA, blocking RNAP II-dependent transcription (Espinoza et al. 2004; Mariner et al. 2008; Yakovchuk et al. 2009, 2011). Another lncRNA, 7SK, is transcribed by RNAP III and has been shown to regulate RNAP II-dependent transcription elongation (Yik et al. 2003; Chen et al. 2004; Peterlin et al. 2012). 7SK lncRNA binds to phosphorylated PTEFb (Chen et al. 2004) and serves as a scaffold to mediate the interaction of HEXIM1 and PTEFb. In this interaction, HEXIM1 inhibits the CTD-kinase activity of PTEFb (Yik et al. 2003; Chen et al. 2004; Peterlin et al. 2012), thereby preventing the phosphorylation of RNAP II and blocking transcription elongation (Yik et al. 2003; Chen et al. 2004; Peterlin et al. 2012). In contrast, stress-inducing agents, such as ultraviolet irradiation and actinomycin D, can dissociate HEXIM1 and 7SK from PTEFb, leading to an increase in nuclear levels of active PTEFb, an effect that may activate stress-induced gene expression (Yik et al. 2003; Chen et al. 2004; Peterlin et al. 2012).

LncRNAs also act as co-factors or inhibitors to regulate the activity of a particular transcription factor. The lncRNA Evf2 is transcribed from the Ei region, one of the two *DLX*-5/6 ultraconserved intergenic enhancer regions (Feng et al. 2006). Evf2 specifically binds to the homeodomain protein DLX-2 and recruits DLX-2 to this same enhancer, resulting in an induction of both *DLX*-5 and -6 expression. This result indicates that Evf2 lncRNA acts as a co-factor of DLX-2 (Feng et al. 2006) (shown in Fig. 2b). Unlike Evf2, NRON lncRNA, as mentioned earlier, binds to the NFAT transcription factor and renders it inactive by preventing its nuclear accumulation, inhibiting the expression of target genes (Sharma et al. 2011).

Post-transcriptional regulation

Another class of ncRNAs, referred to as NATs, are derived from the anti-sense strand of many protein-coding genes (Beltran et al. 2008). The ubiquitous NATs in the human transcriptome and their ability to bind with complementary sequences suggest that they may play a key role in gene expression regulation, especially in the post-transcriptional processing of mRNA, including mRNA editing, splicing, transport, translation and degradation (Beltran et al. 2008; Annilo et al. 2009).

Antisense lncRNAs can mediate alternative splicing of mRNA by forming RNA duplexes. One of these ncRNAs, Zeb2 (zinc finger E-box binding homeobox 2) NAT, overlaps the 5′ splice site in an intron located in the 5′-untranslated region (UTR) of Zeb2 mRNA. Zeb2 NAT can bind Zeb2 mRNA through complementary base-pairing and

prevent the splicing processing of the intron. This event results in the up-regulation of Zeb2 protein without significantly altering the level of Zeb2 mRNA (Beltran et al. 2008) (shown in Fig. 2c). Another study has shown that the natriuretic peptide precursor A (NPPA) also has an antisense partner, NPPA-AS. The *NPPA* gene codes for a precursor of atrial natriuretic peptide (ANP), which protects the cardiovascular system from volume and pressure overload. NPPA-AS lncRNA can bind to NPPA, generating RNA duplexes and displaying a complex pattern of alternative splicing in vivo. This process reduces the levels of the intron-retained NPPA mRNA isoform (Annilo et al. 2009).

lncRNAs in imprinting and X chromosome inactivation (XCI)

Genomic imprinting is an epigenetic phenomenon resulting in a monoallelic, parental-specific expression pattern and an excellent model for understanding how lncRNAs regulate transcriptional gene silencing in *cis*. Although imprinted genes accounts for only a few of the human genome (perhaps less than 1 % of known genes), they paly important roles in growth and development, particularly in higher-order brain processes, such as learning and behavior (Davies et al. 2005; Wilkinson et al. 2007; Bartolomei and Ferguson-Smith 2011). Imprinting is established in *cis* primarily by DNA methylation marks on imprinting control regions (ICRs) in the gametes (Abramowitz and Bartolomei 2012). It has been demonstrated that most imprinted genes are located in clusters and all the well-characterized imprinted clusters contain at least one lncRNA as their partners (Sleutels and Barlow 2002; Mohammad et al. 2009). For the most part, the imprinted genes in each cluster are expressed from the same parental chromosome, whereas the lncRNA is expressed from the other parental chromosome (shown in Fig. 3a) (Barlow and Bartolomei 2014). Generally, lncRNAs functionally implicated in the parental-specific expression of genes can be classified into antisense lncRNAs (Kcnq1ot1, Airn, Nespas, Ube3a-ATS), intergenic lncRNAs (H19, IPW and MEG3 lncRNA) and enhancer RNAs (IG-DMR eRNA) (Barlow and Bartolomei 2014). These imprinted lncRNAs employ diverse molecular mechanisms to control epigenetically regulated transcription across imprinted clusters. Antisense lncRNAs epigenetically regulate expression of multiple genes in imprinted clusters by interacting with and recruiting chromatin-remodeling complexes in a sequence-specific fashion (Kanduri 2015). Enhancer RNAs can regulate genomic imprinting by promoting higher-order chromatin establishment, thereby enabling early replication and inner subnuclear positioning of target locus (Darrow and Chadwick 2013). As for intergenic lncRNAs, it seems that there is no common mechanism being employed by them. For example,
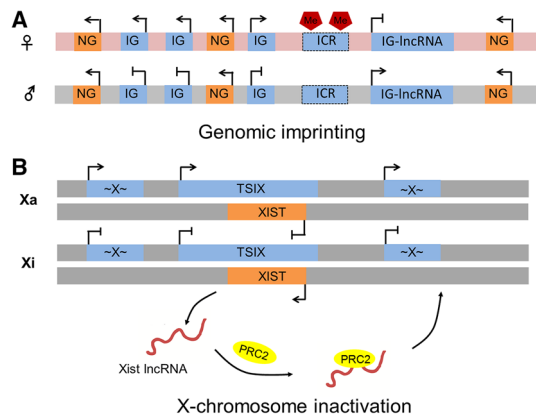
Fig. 3 LncRNAs are involved in genomic imprinting and X chromosome inactivation (XCI). **a** Most imprinted genes (IG) are located in clusters and contain multiple protein-coding genes and at least one lncRNA (IG-lncRNA). Nonimprinted genes (NG) can also be present. Imprinting is established in *cis* primarily by DNA methylation (Me) marks on imprinting control regions (ICRs) in the gametes. One pair of diploid chromosomes is shown: *the pink* is of maternal origin and *the gray* of paternal origin. **b** In female mammalian cells, one of the two X chromosomes is randomly silenced. At around the implantation stage of early embryogenesis, both X chromosomes express the Tsix lncRNA, which negatively regulates its antisense transcript, Xist. On the future active X chromosome (Xa), *TSIX* continue being expressed, and the other allele on the future inactive X chromosome (Xi) is silenced. As a result, *XIST* is de-repressed on the Xi. The Xist lncRNA coats the X chromosome in *cis* and recruits chromatin-remodeling complexes PRC2, which trimethylates lysine 27 on histone H3 (H3k27me3) and induces the formation of heterochromatin, ultimately leading to X chromosome inactivation. X represents most genes on the X chromosome outside of the XIC (color figure online)

IPW, a lncRNA in the critical region of the Prader-Willi syndrome (PWS) locus, may promote a cross-talk between two imprinted clusters through regulating the chromatin structure of an imprinting control region (Stelzer et al. 2014; Kanduri 2015). However, the methylation status of *H19* promoter can regulate *IGF2* expression through affecting the chromatin insulator CTCF binding to the ICR of the cluster (Delaval and Feil 2004).

In mammals, females possess two X chromosomes, however, males have one X and one Y. Thus, a dosage equalization mechanism is necessary for most X-linked genes. XCI occurs randomly in female post-implantation embryonic somatic cells (Autuoro et al. 2014). The molecular mechanisms of XCI are still obscure, but several lncR-NAs have been identified from a 500 kb stretch of DNA at Xq13 known as the X-inactivation center (XIC) (Kanduri 2011). LncRNA X-inactive specific transcript (Xist) and its antisense transcript Tsix are of key importance. Xist lncRNA is expressed exclusively from the *XIST* gene on the inactive X chromosome and is spliced and polyadenylated (Goto and Monk 1998; Pontier and Gribnau 2011). The Xist lncRNA coats the X chromosome in *cis* and recruits

chromatin-remodeling complexes PRC2, which trimethylates lysine 27 on histone H3 (H3k27me3) and induces the formation of heterochromatin, ultimately leading to X chromosome inactivation (Brockdorff 2011; Pontier and Gribnau 2011). Meanwhile, the function of Xist is antagonized by the antisense transcript Tsix lncRNA, which is transcribed from the active X chromosome (Pontier and Gribnau 2011). Tsix may inhibit *XIST* expression by transcriptional interference (Sado et al. 2006) or by recruiting chromatin-remodeling complexes to the *XIST* promoter (Sun et al. 2006). However, another study suggests that Xist and Tsix can form a duplex RNA that is then processed by the RNA interference pathway to generate siRNAs required for depositing chromatin-remodeling complexes (Ogawa et al. 2008; Pontier and Gribnau 2011).

The roles of lncRNAs in complex human diseases

There is increasing interest in the potential role of lncRNAs in the pathogenesis of many human diseases. Moreover, lncRNAs also act as diagnostic or prognostic biomarkers and attractive therapeutic targets for a variety of human conditions, such as cancers, cardiovascular diseases, autoimmune diseases and neurodegenerative disorders.

lncRNAs involved in cancers

A larger number of literatures find that aberrant expressed lncRNAs were involved in the etiology of cancers and tumor metastasis (Serviss et al. 2014). Besides H19, HOTAIR, ANRIL, MALAT1, MEG3,PCGEM1 and PCAT-1, which have been extensively reviewed previously (Maruyama and Suzuki 2012), many newer lncRNAs were found to play a critical regulatory role in the pathogenesis of cancer in recent years (Poliseno et al. 2010; Chen et al. 2015a, b; Nie et al. 2015; Yang et al. 2015a) (Summarized in Table 1).

More recently, the lncRNA PVT1 has been shown to be dysregulated in several cancers, such as hepatocellular carcinoma (HCC) (Wang et al. 2014a), non-small cell lung cancer (NSCLC) (Yang et al. 2014), pancreatic cancer (Huang et al. 2015), gastric cancer (Ding et al. 2014) and acute promyelocytic leukemia (APL) (Zeng et al. 2015). Wang et al. (Wang et al. 2014a) have found that PVT1 was upregulated in HCC and promoted cell proliferation, cell cycling, and stem cell-like properties of HCC cells by enhancing the stability of NOP2, a RNA-binding protein that binds to PVT1. Another study reported that elevated PVT1 expression in APL may result from gain of supernumerary copies of the 8q24 chromosomal region and MYC protein activation in APL cells, which correlated with leukemic cell proliferation (Zeng et al. 2015). The novel

Table 1 Some newer lncRNAs involved in cancers

LncRNAs	Size	Cytoband	Diseases	Biological functions	References
Oncogenic					
Particle	1.42 kb	2p11.2	HCC	Interacts with the Myb proto-oncogene transcription factor, thereby enabling cis regulation of MAT2A transcription	O'Leary et al. (2015) and Yang et al. (2001)
TUC399	1.198 kb	Chr12	HCC	Modulates tumor cell growth and adhesion	Kogure et al. (2013)
TCF7	N/A	Chr5	HCC	Involves in IL-6 induced EMT process, invasion and mobility of HCC cells	Wu et al. (2015)
UCA1	7.375 kb	19p13.12	Bladder cancer, TSCC, melanoma, ESCC, HCC, gastric cancer, NSCLC, ovarian cancer	Regulates cellular migration and invasion	Li et al. (2014a, c), Fang et al. (2014), Tian et al. (2014), Zheng et al. (2015) and Wang et al. (2015a, b, c)
PVT1	>300 kb	8q24	HCC, NSCLC, pancreatic cancer, gastric cancer, APL	Promotes cell proliferation	Wang et al. (2014a), Yang et al. (2014), Huang et al. (2015), Ding et al. (2014) and Zeng et al. (2015)
PRNCR1	12.722 kb	8q24.21	Prostate cancer, CRC	Regulates cell proliferation, cell cycle arrest	Yang et al. (2013a, 2016)
LINC00152	151.438 kb	2p11.2	Gastric cancer, HCC	Participated in cell cycle arrest, apoptosis, EMT, cell migration and invasion	Zhao et al. (2015) and Ji et al. (2015)
NEAT1	22.767 kb	11q13.1	ESCC	Promotes cell proliferation, migration and invasion	Chen et al. (2015c)
SNHG15	3.939 kb	7p13	Gastric cancer	Promotes cell proliferation and invasion via regulating MMP2 and MMP9 expression	Chen et al. (2015b)
MIR31HG	2.166 kb	9p21.3	Gastric cancer,PDAC	Regulates cell proliferation and invasion	Nie et al. (2015) and Yang et al. (2015a)
Tumor suppressive					
TUG1	7.1 kb	22q12.2	NSCLC	A direct downstream target of p53, represses the expression of HOXB7 by binding to PRC2, inhibits cell proliferation	Zhang et al. (2014)
PTENP1	3.9 kb	9p13.3	Prostate, colon, gastric cancer, HCC	Inhibits cell proliferation, migration and invasion	Poliseno et al. (2010), Dong et al. (2015) and Chen et al. (2015a)

HCC hepatocellular carcinoma, *TSCC* tongue squamous cell carcinoma, *ESCC* esophageal squamous cell carcinoma, *NSCLC* non-small cell lung cancer, *APL* acute promyelocytic leukemia, *CRC* colorectal cancer, *PDAC* pancreatic ductal adenocarcinoma, *Myb* myeloblastosis, *MAT2A* methionine adenosyltransferase II, alpha, *EMT* epithelial-mesenchymal transition, *MMP2* Matrix metallopeptidase 2, *MMP9* matrix metallopeptidase 9

lncRNA prostate cancer non-coding RNA 1 (PRNCR1), which has been demonstrated to be associated with prostate cancer susceptibility (Chung et al. 2011; Yang et al. 2013a), is also located in the susceptible genomic area of colorectal cancer (CRC). A latest study has suggested that PRNCR1 was significantly overexpressed in CRC tissues compared with adjacent tissues, which associated with large tumor volume (Yang et al. 2016), Further study found that knockdown of PRNCR1 by a specific antisense oligonucleotide (ASO) induced cell cycle arrest in the G0/G1 phase and a significant decrease in the proportion of cells in the S phases, but did not affect cell apoptosis or invasive ability.

LINC00152 was documented as an important lncRNA participated in cell cycle arrest, apoptosis, epithelial-mesenchymal transition (EMT), cell migration and invasion in gastric cancer (Zhao et al. 2015). Further exploring found that LINC00152 can also exist in blood stably because of its protected by exosomes, indicating that it may act as a circulating biomarker for gastric cancer (Li et al. 2015b). More recently, Zhou et al. (2015) have confirmed that cytoplasmic LINC00152 could directly bind with epidermal growth factor receptor (EGFR) which caused a constitutive expression of EGFR and an activation of PI3K/AKT signaling, then promoting tumor growth. Another study has demonstrated that hypomethylated LINC00152 was upregulated in HCC and induced cell proliferation as well as tumor growth by binding to the promoter of epithelial cell adhesion molecule (EpCAM) through a *cis*-regulation and then activating the mechanistic target of rapamycin (mTOR) pathway (Ji et al. 2015).

Taurine-up-regulated gene 1 (TUG1), a 7.1-kb lncRNA, is generally down-regulated in NSCLC. Decreased TUG1 lncRNA expression was also found to be associated with a higher tumor (T), lymph node (N), metastasis (M) stage and tumor size, as well as poorer overall survival (Zhang et al. 2014). Further experiments revealed that TUG1, as a direct transcriptional target of P53, could epigenetically represses the expression of *HOXB7* (a known oncogene) by binding to PRC2, thus inhibiting cell proliferation in NSCLC. Together, these results suggested that P53-regulated TUG1 lncRNA is a growth regulator that acts partly by controlling *HOXB7*. In addition, the P53/TUG1/PRC2/*HOXB7* network might serve as targets for NSCLC diagnosis and therapy.

Recently, Wu et al. (2015) have demonstrated that a lncRNA TCF7 was induced by IL-6 in a time- and dose-dependent manner through activating STAT3, which was essential for IL-6 induced epithelial-mesenchymal transition (EMT) process, invasion and mobility of HCC cells. LncRNA urothelial cancer-associated 1 (UCA1) was reported to be involved in several type of tumors, including bladder cancer (Li et al. 2014c), tongue squamous cell

carcinoma (TSCC) (Fang et al. 2014), melanoma (Tian et al. 2014), esophageal squamous cell carcinoma (ESCC) (Li et al. 2014a), gastric cancer (Zheng et al. 2015), HCC (Wang et al. 2015a), NSCLC (Wang et al. 2015c) and ovarian cancer (Wang et al. 2015b), mostly by regulating cellular migration and invasion. Recently Xue et al. (2015) have discovered that UCA1 induced EMT of bladder cancer cells by increasing the expression of ZEB1/2, and regulated bladder cancer cell migration and invasion by hsa-miR-145 and its target gene the *FSCN1*.

It has been suggested that interactions of tumor cells in microenvironment are recognized as a critical determinant of the carcinogenesis and promote the invasion and metastasis of tumors (Bissell et al. 2002). Exosomes, as intercellular communication tools originating from endosomal compartments called multivesicular bodies (MVBs), have recently been reported to be important carriers for some lncRNAs that play roles in tumor progression (Wang et al. 2014b; Isin et al. 2015). For example, a recent study has found that intercellular transfer of lncRNA TUC399, which was functionally implicated in modulating tumor cell growth and adhesion, can be mediated by HCC cells-derived exosomes (Kogure et al. 2013). The exosomes-mediated intercellular transfer of TUC399 may be a mechanism by which tumor cells can modulate their local cellular environment. Taken together, functionally active lncRNA molecules can be transferred by exosomes, enabling cells to exert genetic influences on other cells within the microenvironment.

lncRNAs involved in cardiovascular diseases

It is becoming more evident that lncRNAs play important roles in cardiovascular development and diseases. Two recent reports have demonstrated that the two lncRNAs Fendrr and Braveheart (Bvht) are involved in heart development (Grote et al. 2013; Klattenhoff et al. 2013). With the application of high-throughput sequencing techniques, some lncRNAs were found to be master regulators in the pathogenesis of human heart diseases, including myocardial infarction, cardiomyopathy, heart failure, and atherosclerosis (summarized in Table 2).

lncRNAs in myocardial infarction

Ishii et al. (2006) identified and named the lncRNA myocardial infarction associated transcript (MIAT), which might confer a genetic risk of myocardial infarction (MI). The *MIAT* gene has six SNPs, and the minor variant of one SNP (A11741G) caused a 1.3-fold increase in MIAT lncRNA transcriptional level in vitro, with the normal A allele exhibiting tighter binding to an unidentified nuclear factor (Ishii et al. 2006; Schonrock et al. 2012). According

Table 2 Representative lncRNAs involved in cardiovascular diseases

LncRNA	Size	Cytoband	Diseases	Biological functions	References
CARL[a]	N/A	Chr2	I/R	Increases the expression of PHB2 through directly binding to miR-539 and inhibiting its expression	Wang et al. (2014d)
MIAT	≈9 kb	22q12.1	MI	Retinal cell fate specification, SNPs of lncRNA, confers risk of MI	Ishii et al. (2006) and Schonrock et al. (2012)
MIRT1[a]	N/A	Chr19	MI	May attribute to infiltration of inflammatory cells into the heart	Zangrando et al. (2014)
MIRT2[a]	N/A	Chr19	MI	May attribute to infiltration of inflammatory cells into the heart	Zangrando et al. (2014)
LIPCAR	N/A	N/A	MI	Unknown, biomarker	Kumarswamy et al. (2014)
CHRF[a]	N/A	Chr18	Cardiac hypertrophy	Regulates Myd88 expression through repressing miR-489 expression	Wang et al. (2014c)
Mhrt	Splice variants	14q11.2	Cardiac hypertrophy	Sequesters Brg1 from its genomic DNA targets by competitive binding to the helicase domain of Brg1	Han et al. (2014)
APOA1-AS	~20 kb	11q23.3	Coronary heart disease	Inhibits the expression of APOA1 through recruiting chromatin-modifying complexes	Halley et al. (2014)
lincRNA-p21	N/A	6p21.2	Coronary heart disease	Directly binds to MDM2, leads to p53 release from MDM2 and binding to p300, which thereby enhances p53 activity	Wu et al. (2014)
DYN-LRB2-2[a]	~29.1 kb	16q23.3	Coronary heart disease	Promotes cholesterol efflux mediated by ABCA1 and up-regulates GPR119	Hu et al. (2014)
Coromaker	N/A	N/A	Coronary heart disease	Unknown, biomarker	Yang et al. (2015b)

I/R ischemia and reperfusion, *MI* myocardial infarction, *Myd88* myeloid differentiation primary response gene 88, *MDM2* murine double minute 2, *GPR119* G protein-coupled receptor

[a] The experimental subject is mouse

to the results of this study, it is possible that the altered expression of MIAT lncRNA due to this SNP may play a role in MI pathogenesis.

Furthermore, a microarray-based study identified 20 up-regulated lncRNAs and ten down-regulated lncRNAs following MI in mice, among which two specific lncRNAs, MIRT1 and MIRT2, were significantly up-regulated by fivefold and 13-fold, respectively. MIRT1 and MIRT2 were associated with genes involved in left ventricular remodeling (Zangrando et al. 2014).

lncRNAs in ischemia/reperfusion injury

LncRNAs were also studied in the pathology of cardiac ischemia/reperfusion (I/R). Liu et al. (2014) analyzed the expression changes of lncRNAs in the early stage of reperfusion in the mouse infarct region. After ischemia, 64 lncRNAs were up-regulated and 87 lncRNAs were down-regulated among total 31,423 lncRNAs. Specifically, further analysis by the co-expression modules indicated that a down-regulated lncRNA uc007prv.1 was connected to a tumor necrosis factor-alpha-inducible gene, encoding A20

(TNFAIP3) which was reported to be involved in I/R (Yu et al. 2011). PHB2, as a subunit of the prohibition complex, has an important role in inhibiting mitochondrial fission and apoptosis and is abundantly expressed in cardiomyocytes under physiological conditions. Recently, a study reported that the lncRNA cardiac apoptosis-related lncRNA (CARL) can act as an endogenous sponge of miR-539 that targets PHB2 (Wang et al. 2014d). CARL can impair miR-539-dependent PHB2 down-regulation by directly binding to miR-539 and inhibiting its expression upon *I/R*. The ultimate result in a reduction in mitochondrial fission, apoptosis and infract sizes.

lncRNAs in cardiac hypertrophy and heart failure

Clusters of lncRNAs have been associated with cardiac hypertrophy. Recently, Pei et al. (Han et al. 2014) identified a cluster of lncRNA transcripts from the myosin heavychain 7 (*MYH7*) loci, which they termed myosin heavy-chain-associated RNA transcripts (Myheart, or Mhrt). These authors demonstrated a reciprocal Mhrt-Brg1 inhibition feedback circuit that is crucial for heart

function. Brg1, a chromatin-remodeling factor that is activated by pathological stress, can repress *MYH6* and *MHRT* in sense and antisense directions in the heart by occupying their promoter regions. This repression causes a pathological switch of *MYH6/7* expression, contributing to cardiomyopathy. Interestingly, this stress/Brg1-dependent *MYH* switch can be largely eliminated by restoring Mhrt lncRNA to pre-stress levels. In this context, Mhrt lncRNA sequesters Brg1 from its genomic DNA targets by competitive binding to the helicase domain of Brg1, a domain with a dual-binding feature and which is crucial for Brg1′s tethering to chromatinized DNA targets. The studies of these authors thereby identified a cardioprotective lncRNA and established a new paradigm for lncRNA-chromatin interactions. Another research has identified a lncRNA termed cardiac hypertrophy related factor (CHRF), which regulates myeloid differentiation primary response gene 88 (*MYD88*) expression and consequent cardiac hypertrophy by repressing miR-489 expression (Wang et al. 2014c).

lncRNAs in coronary heart diseases

Apolipoprotein A-1 (APOA-1), which plays an important role in cholesterol efflux, is the major protein component of high-density lipoprotein (HDL) in plasma (Fatemi et al. 2014). Halley et al. (2014) have identified an endogenously expressed lncRNA, APOA1-AS, that can negatively regulate *APOA1* through the recruitment of chromatin-modifying complexe. These authors found that knockdown of APOA1-AS up-regulated *APOA1* both in vitro and in vivo, with increased active H3K4met3 marks and decreased repressive H3K27met3 in the promoter and enhancer regions of the *APOA1* gene. The knockdown of APOA1-AS caused a reduction in the chromatin binding of lysine (*K*)-specific demethylase 1 (LSD1) and suppressor of zeste 12 (SUZ12) protein, a key component of the PRC2 complex. This study suggested that targeting APOA1-AS may have therapeutic potential in protecting against coronary heart disease. Similarly, a mouse study found that oxidized low-density lipoproteins (LDLs) stimulated an lncRNA called DYN-LRB2-2, which promoted cholesterol efflux mediated by a transmembrane transport protein functions to transport cellular cholesterols to its corresponding apolipoproteins (ABCA1) and up-regulated G protein-coupled receptor 119 (GPR119), which regulated atherosclerotic plaque formation by decreasing cellular cholesterol levels and inflammation (Hu et al. 2014).

Another lncRNA associated with coronary heart disease is lincRNA-p21, which was observed to be down-regulated in patients with coronary artery disease. In a recent study, lincRNA-p21 was identified as a key regulator of cell proliferation and apoptosis during atherosclerosis (Wu et al. 2014). The authors showed that lincRNA-p21 repressed cell proliferation, neointima formation and induced apoptosis by directly binding to mouse double minute 2 (*Mdm2*). This binding leads to P53 release from *Mdm2* and its binding to P300, thereby enhancing P53 activity.

lncRNAs and autoimmune diseases

In recent years, a few of lncRNAs have been identified in the context of autoimmune diseases, suggesting that lncRNAs may be involved in the pathogenesis of these conditions (Table 3).

lncRNAs in systemic lupus erythematosus (SLE)

SLE is a chronic systemic autoimmune disease characterized by the production of multiple autoantibodies, complement activation and immune-complex deposition, resulting in widespread tissue damage (Zhao et al. 2010). Recently, a lncRNA GAS5 has been linked with increased susceptibility of SLE in mouse models, presumably as a result of its effect on the immunosuppressant role of glucocorticoids (Kino et al. 2010). Since suppressed GAS5 may inhibit cell cycle and apoptosis, it is implicated in autoimmune diseases by leading promotion antigen exposure and production of autoantibodies (Coccia et al. 1992; Haywood et al. 2006).

lncRNAs in rheumatoid arthritis (RA)

RA is a systemic autoimmune disorder characterized by chronic inflammation of synovial tissue (ST) that results in irreversible destruction of small to medium size joints (Smolen et al. 2007). LncRNA H19, as discussed above, may act as both a tumor suppressor and oncofetal gene. More interestingly, a previous study has reported that H19 lncRNA may also play an important role in RA (Stuhlmuller et al. 2003). Stuhlmuller et al. found that H19 lncRNA was significantly overexpressed in ST of RA patients relative to normal/joint trauma controls. Moreover, H19 lncRNA exhibited increased sensitivity to starvation/cytokine regulation in RA (Stuhlmuller et al. 2003).

Recently, Muller et al. (2014) have found that lincRNA (used total number, 7.419 lincRNA) was regulated by TNFα and superior to IL-6 in CD14 monocytes in human subjects with RA. These cytokines have a specific correlation with lincRNA transcription. Therefore, the interregulation of lincRNA may be important intracellular molecular effectors of different cytokines in cells of innate immune system in the context of RA.

Table 3 Representative lncRNAs involved in autoimmune diseases

LncRNA	Size	Cytoband	Diseases	Biological functions	References
GAS5	0.6–1.8 kb	1q25.1	SLE	Associates with increased susceptibility of SLE	Haywood et al. (2006) and Kino et al. (2010)
SAS-ZFAT	2.619 kb	8q24.22	AITD	May play a critical role in B cell function by affecting the expression of truncated ZFAT and determine susceptibility to AITD	Shirasawa et al. (2004)
H19	2.3 kb	11p15.5	RA	May be an indicator of physiological/pathological stress situations	Stuhlmuller et al. (2003)
PRINS	8.925 kb	10p12.1	Psoriasis	May play a protective role in cells exposed to stress and contribute to psoriasis susceptibility	Sonkoly et al. (2005)
lncRNA G36220	N/A	N/A	Psoriasis	Unknown, differentially expresses in psoriatic skin and locates within a psoriasis susceptibility locus TNFAIP3	Tsoi et al. (2015)
THRIL	1.98 kb	12q24.31	Kawasaki disease	Regulates TNF-α transcription by interacting with hnRNPL	Li et al. (2014b)

SLE systemic lupus erythematosus, *AITD* autoimmune thyroid disease, *RA* rheumatoid arthritis, *hnRNPL* heterogenous nuclear ribonucleoprotein L

lncRNAs in psoriasis

A previous study reported that the lncRNA Psoriasis susceptibility-related RNA Gene induced by stress (PRINS) is essential in the survival of keratinocytes under stress conditions and may contribute to psoriasis susceptibility (Sonkoly et al. 2005). Recently, Tsoi et al. (2015) identified and characterized the expressed lncRNAs in lesional psoriatic, uninvolved psoriatic and normal skin biopsies by RNA-seq. These authors detected 2942 previously annotated and 1080 novel lncRNAs that are expected to be skin specific. Notably, over 40 % of the novel lncRNAs, such as lncRNAs G2608, G25746, and G36220 (a differentially expressed lncRNA (ENSG00000237499) in psoriatic skin and located within a psoriasis susceptibility locus TNFAIP3), are differentially expressed in psoriatic lesions versus uninvolved or normal skin. This study implicates many lncRNAs in the immunopathogenesis of psoriasis and provides a resource for lncRNA studies in other autoimmune diseases.

lncRNAs in autoimmune thyroid disease (AITD)

AITD, including Graves disease (GD) and Hashimoto's thyroiditis (HT), is caused by an autoimmune response to selfthyroid antigens and has a significant genetic component. LncRNA SAS-ZFAT (small antisense transcript of *ZFAT*) is a CD19+B cell-specific antisense transcript. Shirasawa et al. (2004) discovered that the T allele of SNP Ex9b-SNP10, located in intron 9 of *ZFAT* and the promoter region of *SAS-ZFAT*, is associated with an increased risk for AITD. Further studies demonstrated that an unknown nuclear factor binds more tightly to the Ex9b-SNP10-T-associated *ZFAT*-allele. This binding results in the repression of *SAS-ZFAT* expression, which inversely affects the expression level of its sense counterpart, truncated *ZFAT*.

lncRNAs in other autoimmune diseases

Li et al. (2014b) have identified a lncRNA named TNFα and hnRNPL related immunoregulatory LincRNA (THRIL), which bound specifically to heterogenous nuclear ribonucleoprotein L (hnRNPL) and formed a functional THRIL–hnRNPL complex that regulated basal and stimulated transcription of TNFα gene by binding to its promoter. In activated cells, high levels of TNFα secretion initiated a negative feedback loop in which THRIL and, in turn, TNFα expression is down-regulated. Interestingly, they found that THRIL expression was clearly lower during the acute phase of Kawasaki disease during which TNFα levels were elevated. This effect mirrored the negative feedback loop of THRIL regulation demonstrated in previous vitro experiments and suggested that THRIL could be a novel biomarker for immune activation.

lncRNAs involved in neurological diseases

The human brain is one of the most complex biological systems, and recent studies have emphasized an important role for lncRNAs in the development and function of the nervous system, highlighting the functional importance of this subclass of non-coding RNAs in neurological diseases (Table 4).

lncRNAs and neurodegeneration

In a study of Alzheimer's disease (AD), Faghihi et al. (2008) identified a conserved noncoding antisense transcript for β-secretase-1 (BACE1), a crucial enzyme for the accumulation of amyloid-β 1–42 (Aβ 1–42) that plays a key role in the pathogenesis of Alzheimer's disease. The antisense transcript (lncRNA BACE1-AS) rapidly and reversibly up-regulates BACE1 levels by increasing BACE1 mRNA stability in response to a variety of cell stresses, including Aβ1–42 exposure; this effect results in additional Aβ1–42 production. Subsequently, increased Aβ1–42 levels further increase BACE1-AS expression through a post-transcriptional feed-forward mechanism (Faghihi et al. 2008). In addition, Faghihi et al. also found that treatment with BACE1-AS siRNA can abolish stress-induced increases in BACE1 expression without disturbing physiologically essential expression levels. Consequently, the authors proposed that BACE1-AS may be a perfect biomarker and therapeutic target in Alzheimer's disease (Faghihi et al. 2008). Another lncRNA that was found to be dysregulated in AD was brain cytoplasmic 200 (BC200) RNA, a translational regulator that is selectively targeted to the somatodendritic domains of neurons (Mus et al. 2007). BC200 levels were found to be up-regulated in brain areas that are affected in AD, such as Brodmann's area 9 and the hippocampus. Relative BC200 levels in those areas increased in parallel with disease severity. Moreover, in more advanced stages of AD, BC200 was mislocalized and clustered in the perikaryon. These observations suggested a potential role of this dendritic lncRNA in the synaptodendritic deterioration that occurs in AD.

Spinocerebellar ataxia type 8 (SCA8) is characterized by bidirectional transcription of the CTG/GAG expansion repeat, which produces both (1) a lncRNA transcript containing a CUG expansion (CUG^{exp}), ATXN8OS; and (2) a polyglutamine expansion protein encoded by the ATXN8 CAG expansion (CAG^{exp}) transcript, which is transcribed in the opposite direction (Moseley et al. 2006). A recent study found that the expanded ATXN8OS transcripts accumulated as ribonuclear inclusions that co-localized with the splicing factor MBNL1 in a subset of neurons in SCA8 patients and mice (Daughters et al. 2009). In addition, ATXN8OS transcripts induced splicing changes and increased the expression of a CUGBP1-MBNL1-regulated CNS target, GABA-A transporter 4 (Gabt4). This transporter is associated with the loss of GAB Aergic inhibition within the granular cell layer (Daughters et al. 2009). Together, these results suggested that the expanded ATXN8OS transcripts can alter the activities of alternative splicing factors through an RNA gain-of-function mechanism, contributing to SCA8 pathogenesis.

To elucidate the lncRNA network changes in Huntington's disease (HD), Johnson (2012) have mined existing microarray data (Hodges et al. 2006) to identify seven new lncRNAs that were dysregulated in HD brains. Three of them were novel, among which LINC00341 and RPS20P22 were elevated in HD compared to controls, whereas LINC00342 was decreased. The four known lncRNAs changed significantly in the brains of HD patients including TUG1 and NEAT1 (which were upregulated in HD) and MEG3 and DGCR5 (which were downregulated). Interestingly, several of these lncRNAs contained genomic binding sites for RE1 Silencing transcription factor (REST), a key mediator of transcriptional changes in HD, including the known REST target lncRNA, DGCR5. Similarly, a separate study showed that the HAR1 lncRNA locus (including both HAR1F and HAR1R transcripts) was a direct target

Table 4 Representative lncRNAs involved in central nervous system diseases

LncRNA	Size	Cytoband	Diseases	Biological functions	References
BACE1-AS	~2 kb	11q23.3	AD	Increases BACE1 mRNA stability	Faghihi et al. (2008)
BC200	13.458 kb	2p21	AD	May play a role in synaptodendritic deterioration of AD	Mus et al. (2007)
ATXN8OS	32 kb	13q21	SCA8	A toxic gain of function at RNA level; causes splicing changes and increased expression of Gabt4	Moseley et al. (2006) and Daughters et al. (2009)
HAR1	N/A	N/A	HD	Influences genes promoting aberrant nuclear-cytoplasmatic trafficking of *REST* gene	Johnson et al. (2010)
FMR4	2.4 kb	Xq27.3–28	FXS	Antiapoptotic function, function in FXS is unknown	Khalil et al. (2008)
Gomafu/MIAT	≈9 kb	22q12.1	SZ	May act as a splicing factor scaffold	Barry et al. (2014)
MSNP1AS	3.9 kb	5p14.1	ASD	Associates with the susceptibility of ASD	Kerin et al. (2012)

AD Alzheimer disease, *SCA8* spinocerebellar ataxia type 8, *HD* Huntington's disease, *FXS* fragile X syndrome, *SZ* schizophrenia, *ASD* autism spectrum disorder

of REST, and that the expression of HAR1 lncRNA was significantly reduced in the brains of HD patients (Johnson et al. 2010).

lncRNAs and neurodevelopmental/neuropsychiatric disorders

Fragile X syndrome (FXS) is caused by the expansion of CGG trinucleotide repeats in the 5′UTR of the fragile X mental retardation 1 (*FMR1*) gene, which encodes the crucial neuronal development protein FMRP. The expansion of CGG repeats to above 200 leads to promoter methylation and consequently to the repression or silencing of the *FMR1* gene (Garber et al. 2006; Khalil et al. 2008). A recent study identified the lncRNA FMR4, the transcription of which is initiated upstream and likely shares a bidirectional promoter with *FMR1* (Khalil et al. 2008). The researchers found that FMR4 lncRNA was silenced in Fragile X patients. In addition, FMR4 lncRNA was determined to markedly affect cell survival given that its overexpression increased cell proliferation while its downregulation induced apoptosis. Thus, the silencing of FMR4 lncRNA in the neurons of Fragile X patients might contribute to the pathogenesis of this disease.

Schizophrenia (SZ) is a complex disease that has been associated with alternative splicing (Morikawa and Manabe 2010). Recently, Barry et al. (2014) demonstrated that the lncRNA Gomafu (also known as MIAT and RNCR2), which localized to a novel nuclear compartment consisting of pre-mRNA splicing factors, was involved in alternative splicing of the SZ pathology-related genes *DISC1* (disrupted in schizophrenia 1) and *4ERBB4* (v-erb-a erythroblastic leukemia viral oncogene homolog). These studies functionally link activity-regulated lncRNAs and alternative splicing in neuronal function and open up new avenues for potential SZ therapies that target lncRNA (Barry et al. 2014).

Autism spectrum disorder (ASD), whose pathophysiology is poorly understood, refers to a heterogeneous group of neurodevelopmental disorders characterized by defects in social interactions, language, and behavioral flexibility (Geschwind 2008). A GWAS conducted by Kerin et al. (2012) identified a SNP associated with ASD in a gene-poor region of chromosome 5p14.1. This *locus* was found to encode a 3.9 kb lncRNA (named MSNP1AS) antisense to moesin pseudogene 1 (*MSNP1*), which shows no evidence of being transcribed in the sense orientation. The SNP-containing MSNP1AS transcript was highly overexpressed in post-mortem cerebral cortex of patients with ASD and regulated expression of moesin protein (a known regulator of nuclear architecture (Paglini et al. 1998) in human cells lines, suggesting a possible role in ASD pathophysiology.

The potential of lncRNAs as biomarkers and therapeutic targets

As introduced previously, lncRNAs show higher tissue specificity compared with mRNAs and miRNAs and are significantly dysregulated expression in a wide range of diseases. In addition, they are detectable in tissue and body fluids steady. These features make lncRNAs very suitable as biomarkers. In recent years, most of lncRNAs biomarkers have been identified in many kinds of cancers and cardiovascular diseases.

As aberrant regulation of lncRNAs promotes tumor formation, progression and metastasis, they may be attractive novel biomarkers and therapeutic targets for cancers (Ge et al. 2013; Ishibashi et al. 2013; Konishi et al. 2015; Shi et al. 2015; Tian and Xu 2015; Walsh et al. 2014; Wei and Niu 2015; Yan et al. 2015). On the one hand, lncRNAs with differential expressions in tumor tissues can be used as biomarkers (Chen et al. 2015c; Guo et al. 2015; Ellinger et al. 2015; Liu et al. 2015b). For example, lncRNA PVT1, which was up-regulated in human gastric cancer, was identified as a new biomarker for gastric cancer and may indicate lymph node invasion (Ding et al. 2014). LncRNA ABHD11-AS1 (*ABHD11* Antisense RNA 1) expression was significantly increased in gastric cancer compared with adjacent non-tumor tissues, indicating its potential to be a biomarker for the diagnosis of gastric cancer (Lin et al. 2014). Prensner et al. (2014) have identified and validated high expression of lncRNA SChLAP1 as significantly prognostic for metastatic disease progression of prostate cancer, suggesting the potential of SChLAP1 as a biomarker for treatment intensification in aggressive prostate cancer.

On the other hand, circulating lncRNAs may be extremely suitable as noninvasive biomarkers for cancers. For example, HULC and LINC00152 are novel plasma biomarkers in predicting diagnosis of HCC (Li et al. 2015a). GAS5 may be a plasma biomarker in breast cancer for assessing the surgical effects (Han et al. 2015). PTENP1 are serum diagnostic markers for gastric cancer (Dong et al. 2015). PCA3 (DD3) (Nilsson et al. 2009) and TRPM2-AS (Orfanelli et al. 2015) are urine biomarkers for prostate cancer. Recently, Tong et al. (2015) have identified lncRNA POU3F3 as a novel plasma biomarker for diagnosis of ESCC, and the combination of POU3F3 and serum squamous cell carcinoma antigen (SCCA) was more efficient for ESCC detection, in particular for early tumor screening. Another research has reported three lncRNAs including RP11-397D12.4, AC007403.1, and ERICH1-AS1 as potential biomarkers for predicting the tumorigenesis of NSCLC in the future (Tang et al. 2015). More biomarkers for various tumors were summarized in Table 5.

Since tissues of heart and vascular are difficult to obtain from patients of cardiovascular diseases, the identified biomarkers are mainly circulating lncRNAs (Van Roosbroeck et al. 2013). For instance, the mitochondrial lncRNA LIP-CAR, which showed decreased expression early after myocardial infarction but increased expression during later stages, was identified as a novel plasma biomarker for cardiac remodeling and predicts future death in patients with heart failure (Kumarswamy et al. 2014). LncRNA Coromaker was increased in the plasma of coronary artery disease (CAD) patients with a 92 % specificity and was very stable in plasma samples due to their contained in the plasma extracellular vesicles (Evs), making it a stable, sensitive and specific biomarker for CAD (Yang et al. 2015b).

LncRNAs also have widespread application prospects in the targeted therapies. Chemically synthetic oligonucleotides that have been proven to be effective for targeting endogenous miRNAs in mice also have potential applications in lncRNAs-related therapies (Wang et al. 2012; Cai et al. 2015). For example, systemically administered ASOs in mice effectively knocked down the lncRNA MALAT1 in muscles, correcting myotonic dystrophy in vivo (Wheeler et al. 2012). Recently, Meng et al. (2015) developed a potential therapeutic intervention for AS by reducing UBE3A-ATS with ASOs and inducing a re-expression of *UBE3A* at both the RNA and protein level. In addition, preventing the interaction of lncRNAs with their target proteins may represent another therapeutic avenue. For example, the administration of an "antagolinc" against HOTAIR would lead to competitive inhibition of a chromatin-remodeling complex, such as PRC2, by binding to the lncRNA. This inhibition would normalize the chromatin state to inhibit cancer cell growth and metastasis (Tsai et al. 2011). Recently, lncRNAs related to tumor chemotherapy resistance were reported. Reversing the expression of these lncRNAs in tumors may improve tumor chemoresistance. For example, both HOTAIR (Hutzelmann et al. 2000) and AK126698 (Yang et al. 2013b) lncRNAs participate in resistance to cisplatin in NSCLC. Effective inhibitors that down-regulate HOTAIR expression or sensitize AK126698 may be efficient therapeutic interventions for alleviating cisplatin resistance in NSCLC patients. Taken together, these recent advances indicate a significant potential in developing lncRNA-mediated diagnostics and therapies.

Techniques of identifying lncRNAs deregulated in human diseases

As lncRNAs are highly abundant in mammals and have been demonstrated to play important roles in many biological processes and diseases, there has been an ever increasing need to develop accurate detecting methods for deregulated lncRNAs in human diseases. So far, lncRNA detection technologies are mainly devided into two categories: high throuput technologies mainly including lncRNA microarray and next-generation RNA-seq, and gene-specific detection methods such as RT-qPCR and Northern blot.

LncRNA microarray technique is designed for the global profiling of human lncRNAs and mRNAs, which can identify the lncRNAs involved in known signaling pathways according to the relevant mRNA expression changes in different diseases and control samples (Wang et al. 2015d). Next-generation RNA-seq enables non-biased, high throughput, probe-independent inspection of expression data and high coverage and quantification of global transcript levels as well as the detection of expressed exons and junctions given a sufficient sequencing depth (Soreq et al. 2015). All RNA-seq experiments follow a similar protocol, during which total RNA is isolated from a sample of interest prior to preparing an lncRNA library, and ultimately produce one read in a single-end sequencing reaction or two ends separated by an unsequenced fragment in paired-end reactions (Mortazavi et al. 2008). Recently, researchers proposed a target RNA-seq technology named RNA capture sequencing (RNA CaptureSeq), which integrated current gene capture techniques and the latest deep sequencing technology (Mercer et al. 2012; Clark et al. 2015). This technology can identify and characterize unannotated transcripts whose rare or transient expression is below the detection limits of conventional sequencing approaches (Mercer et al. 2012).

Besides custom RT-qPCR and in situ hybridization (ISH), there are several more advanced technologies for deregulated lncRNAs in human diseases. For example, Yue et al. (2014) have reported a new technique combining RNA fluorescent in situ hybridization (FISH) with immunofluorescence (immuno-FISH), that can be employed at the single cell level to detect the spatial dynamics of specific lncRNA localization with simultaneous insight into the localization of proteins, epigenetic modifications and other details which can be highlighted by immunofluorescence. Eissa et al. (2015) have developed a PCR-free nanoparticle-based specific hybridization assay for direct detection of lncRNA urothelial carcinoma associated-1 (UCA1). Very recently, Liu et al. (2015a) also proposed a novel strategy based on Pt–Pd bimetallic nanodendrites/nanoflower-like clusters on graphene oxide/Au/horseradish peroxidase (PtPd BND/BNF@GO/Au/HRP) to enhance the catalytic efficiency and sensitivity. These strategies may provide more advanced selections for identifying lncRNAs in clinical tissues.

Table 5 LncRNAs as potential biomarkers in cancers and cardiovascular diseases

LncRNA	Full name	Source	Application	Diseases	References
ABHD11-AS1	ABHD11 Antisense RNA 1	Tissue	Diagnosis biomarker	Gastric cancer	Lin et al. (2014)
PVT1	Plasmacytoma variant translocation 1	Tissue	Diagnosis biomarker	Gastric cancer	Ding et al. (2014)
SChLAP1	SWI/SNF complex antagonist associated with prostate cancer 1	Tissue	Prognostic biomarker	Prostate cancer	Prensner et al. (2014)
PCAT-1	Prostate cancer-associated ncRNA transcripts 1	Tissue	Prognostic and diagnosis biomarker	CRC, ESCC, HCC, prostate cancer	Walsh et al. (2014), Ge et al. (2013), Shi et al. (2015) and Yan et al. (2015)
HOTAIR	HOX antisense intergenic RNA	Tissue	Prognostic biomarker	Metastatic breast cancer, CRC, HCC, GISTs, pancreatic cancer	Ishibashi et al. (2013) and Van Roosbroeck et al. (2013)
MALAT1	Metastasis associated in lung adenocarcinoma transcript 1	Tissue or plasma	Prognostic biomarker	NSCLC, HCC, breast cancer, pancreatic cancer, CRC, prostate cancer, osteosarcoma, bladder cancer	Tian et al. (2015), Konishi et al. (2015) and Wei et al. (2015)
Lnc-ZNF180-2	/	Tissue	Prognostic biomarker	ccRCC	Ellinger et al. (2015)
NEAT1	Nuclear paraspeckle assembly transcript 1	Tissue	Prognostic biomarker	ESCC	Chen et al. (2015c)
DANCR	Differentiation antagonizing non-protein coding RNA	Tissue	Prognostic biomarker	CRC	Liu et al. (2015b)
FTX	FTX transcript, XIST regulator	Tissue	Prognostic biomarker	CRC	Guo et al. (2015)
HULC	Highly upregulated in liver cancer	Plasma	Diagnosis biomarker	HCC	Li et al. (2015a)
LINC00152	Long intergenic non-protein coding RNA 152	Plasma	Diagnosis biomarker	HCC	Li et al. (2015a)
GAS5	Growth arrest specific 5	Plasma	Biomarker for assessing the surgical effects	Breast cancer	Han et al. (2015)
POU3F3	POU class 3 homeobox 3	Plasma	Diagnosis biomarker	ESCC	Tong et al. (2015)
PTENP1	Phosphatase and tensin homolog pseudogene 1	Serum	Diagnosis biomarker	Gastric cancer	Dong et al. (2015)
PCA3/DD3	Prostate cancer 3 or differential display code 3 long ncRNA	Urine	Diagnosis biomarker	Prostate cancer	Nilsson et al. (2009)
TRPM2-AS	TRPM2 antisense RNA	Urine	Prognostic biomarker	Prostate cancer	Orfanelli et al. (2015)
UCA1	Urothelial cancer-associated 1	Urine	Diagnosis biomarker	Bladder cancer	Li et al. (2014c) and Xue et al. (2015)
ERICH1-AS1	ERICH1 antisense RNA 1	Blood	Prediction biomarker	NSCLC	Tang et al. (2015)
LIPCAR	LncRNA uc022bqs.1	Plasma	Prediction biomarker for cardiac remodeling and future death in patients with heart failure	MI	Kumarswamy et al. (2014)
Coromaker	LncRNA AC100865.1	Plasma	Diagnosis biomarker	Coronary artery disease	Yang et al. (2015b)

HCC hepatocellular carcinoma, *ESCC* esophageal squamous cell carcinoma, *NSCLC* non-small cell lung cancer, *CRC* colorectal cancercc, *RCC* clear cell renal cell carcinoma, *GISTs* gastrointestinal stromal tumors, *MI* myocardial infarction, *CAD* coronary artery disease

Perspectives

Due to the diversity of lncRNAs function and their important roles in a wide range of diseases, lncRNAs have become the focuses of scientists. Correspondingly, the field of lncRNAs is rapidly evolving with numerous novel lncRNA molecules discovered covering a variety of biological and cellular processes. Although several breakthroughs in understanding the mechanisms and roles of lncRNAs have occurred, researchers are still striving to identify novel lncRNAs and their associated molecules using bioinformatics and high-throughput sequencing technologies. However, there remain significant gaps in our understanding of this RNA species. First, we have only hit the tip of the iceberg as only a handful of mammal lncRNAs involved in diseases have been identified in robust genetic models, and their roles in diseases are obscure. So, it's urgent to identify more diseases-related lncRNAs and clarify their acting mechanisms. Development of unbiased genetic screens, systematic identification of lncRNA expression patterns, as well as a characterization of the lncRNAs themselves and their associated proteins, should pave the way towards this issue. Second, lncRNAs are fast becoming novel targets for gene therapy because of their large number and broad means of gene expression regulation. For instance, ASOs, siRNA and 'antagolinc' have been used to target diseases-associated lncRNAs for therapeutic purpose. However, there are still a lot of challenges to overcome: there is no mature gene therapy means based on lncRNAs as yet, and many technologies have their defects, with delivery and stability issues being the most common difficulties. So, it's necessary to overcome these challenges and develop better therapeutic technologies for exploring lncRNAs-based therapies to a greater degree, which ultimately unveil their utility as novel diagnostic and therapeutic strategies in human complex diseases. Third, given the fact that lncRNAs can mediate epigenetic regulation of gene expression by recruiting chromatin-remodeling complexes to specific locations in the genome, they may have potentials to be novel epigenetic intervention tools for specific sites within the genome. Exploring lncRNAs-based epigenetic intervention tools will provide a new landscape for research and therapy of human complex diseases which involve epigenetic mechanisms. Taken together, further comprehensive study of lncRNAs will provide new answers to old questions in evolution, development as well as disease diagnostics and therapeutics.

Compliance with ethical standards

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