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Long noncoding RNAs as Organizers of Nuclear Architecture

Lu Cheng, Hui Ming, Minzhe Zhu & Bo Wen*

Department of Biochemistry and Molecular Biology and Key Laboratory of Metabolism and Molecular Medicine of Ministry of Education & Institutes of Biomedical Sciences, Shanghai Medical College, Fudan University, Shanghai 200032, China

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In the eukaryotic cell nucleus, chromatin and its associated macromolecules must be organized into a higher-ordered conformation to function normally. However, mechanisms underlying the organization and dynamics of the nucleus remain unclear. Long noncoding RNAs (lncRNAs), i.e., transcripts longer than 200 nucleotides with little or no protein-coding capacity, are increasingly recognized as important regulators in diverse biological processes. Recent studies have shown that some lncRNAs are involved in various aspects of genome organization, including the facilitation of chromosomal interactions and establishment of nuclear bodies, suggesting that lncRNAs act as general organizers of the nuclear architecture. Here, we discuss recent advances in this emerging and intriguing field.

long noncoding RNAs, chromatin, nuclear architecture

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INTRODUCTION

The eukaryotic genome is not linear, but packed into a three-dimensional (3D) confirmation to execute its function. In the interphase nucleus, chromatin forms higher-order structures, such as inter (intra)-chromosomal loops and macro-scale chromatin domains (Bickmore, 2013). Furthermore, DNA, RNA, and proteins can be assembled into non-membranous and highly dynamic nuclear bodies, including the nucleolus, nuclear speckle, paraspeckle, and etc. (Sleeman and Trinkle-Mulcahy, 2014). Meanwhile, the positioning of chromatin and regulatory factors is not random, but is associated with specific nuclear compartments, such as the nuclear periphery (Cremer and Cremer, 2010). This well-patterned nuclear architecture is essential to coordinate the regulation of genome functions. However, mechanisms underlying the formation and maintenance of the nuclear architecture, and its dynamics in development and diseases remain poorly understood.

For a long time, biological research has taken cues from the central dogma and focused on protein-coding genes. However, with rapid advances in functional genomics, it has become clear that only ~1.5% of the human genome encodes proteins, whereas 70%–90% of the genome can be transcribed into many kinds of non-coding RNAs (Consortium, 2012; Kapranov et al., 2007; Okazaki et al., 2002). Among these, the long non-coding RNAs (lncRNAs), which are longer than 200 nucleotides, have received a great deal of attention, and thousands of lncRNAs have been identified in the past few years. These lncRNAs show strong spatial and temporal expression specificity, and are involved in diverse biological processes via interactions with other biological molecules, including proteins, DNA, messenger RNAs (mRNAs), and microRNAs (Guttman and Rinn, 2012; Lee, 2012; Rinn and Chang, 2012; Song et al., 2014).

Decades ago, it was noted that the digestion or inhibition of nuclear RNAs leads to the disruption of chromatin organization (Nickerson et al., 1989). In addition, a tran-

*Corresponding author (email: bowen75@fudan.edu.cn)

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scriptome analysis indicated that lncRNAs are highly enriched in the nucleus (Cheng et al., 2005). Subsequent studies have identified some lncRNAs, such as Xist and Neat1, as key regulators of nuclear organization. Recent evidence has demonstrated that lncRNAs may serve as general organizers in many aspects of nuclear architecture (Batista and Chang, 2013). Here, we discuss advances in this emerging and intriguing field.

lncRNAs MEDIATE CHROMATIN INTERACTIONS

In interphase cell nuclei, chromatin domains interact extensively within or across chromosomes. Enhancer-promoter interactions are recognized as an important mechanism to regulate gene expression. Some lncRNAs have recently been found to participate in interactions at different levels of chromatin organization (Figure 1).

Intra-chromosomal interactions

Enhancers are intergenic or intragenic DNA regulatory elements, and are crucial to control spatiotemporal gene expression during development. Enhancers can be bound with activators and marked with specific histone modifications, including H3K4me1, H3K27ac, and H3K9ac. Recently, a new category of lncRNAs transcribed from active enhancers was identified, and these enhancer-templated non-coding RNAs (eRNAs) are positively associated with their neighboring protein-coding genes (De Santa et al., 2010; Kim et al., 2010; Wang et al., 2011a). For example, in human macrophages treated with endotoxin or breast cancer cells treated with estradiol, after eRNAs were induced, the transcription of their target genes is activated (De Santa et al., 2010; Hah et al., 2013). Recent studies have also identified a series of eRNAs involved in the regulation of immune processes and inflammatory responses (Hah et al., 2015; Ne et al., 2014). Interestingly, a class of lncRNAs shows enhancer-like functions, although they are not necessarily transcribed from enhancers (Orom et al., 2010).

Several studies have proposed that eRNAs or lncRNAs may facilitate chromosome looping between enhancers and their target promoters (Figure 1A). For example, in estradiol-treated MCF7 cells, DNA loops can be induced between enhancers and promoters as detected by a 3D-DSL (3D DNA selection and ligation) assay or ChIA-PET (chromatin interaction analysis by paired-end tag sequencing), and the down-regulation of eRNAs reduces the looping and the expression of its target genes (Hah et al., 2013; Li et al., 2013). Similarly, ncRNA-a elements interact with mediator complexes and activates expression via looping with its target genes (Lai et al., 2013). However, a recent study indicated that eRNAs do not affect enhancer-promoter interactions, but act as decoy for the negative elongation factor (NELF) to activate the expression of nearby genes in neurons (Schaukowitch et al., 2014), suggesting multiple mechanisms of eRNAs.

In addition to eRNAs, other kinds of lncRNAs are involved in intra-chromosomal interactions. The lncRNA HOTTIP, located at the 5′ end of the HoxA (homeobox A) cluster, was reported to contact target genes via chromosome looping, and initiates H3K4me3 modifications by interacting with the WDR5/MLL complex. This lncRNA is necessary and sufficient to activate the transcription of adjacent *HoxA* genes, although the overall chromatin conformation is not affected by its depletion (Wang et al., 2011b). A recent study based on chromatin conformation capture technology (3C) found that the 5′ end of the lncRNA Kcnq1ot1 mediates the formation of long-range chromosomal looping between KvDMR1 and the Kcn1q1 promoter, and maintains allele-specific silencing of Kcn1q1 by recruiting EZH2, a methyltransferase of H3K7me3. Decreased Kcn1q1ot1 expression disturbs the formation of chromosome loops and results in a loss of Kcnq1 imprinting (Zhang et al., 2014). Recently, Xiang et al. identified a lncRNA, CCAT1-L, expressed from a super enhancer 515 kb upstream of MYC (Xiang et al., 2014). CCAT1-L is required for the long-range interaction between this super enhancer and a MYC promoter via an interaction with CTCF, a key organizer of the genome (Xiang et al., 2014). Therefore, the formation of long-range intra-chromosomal looping should be a general mechanism by which lncRNAs regulate chromatin status.

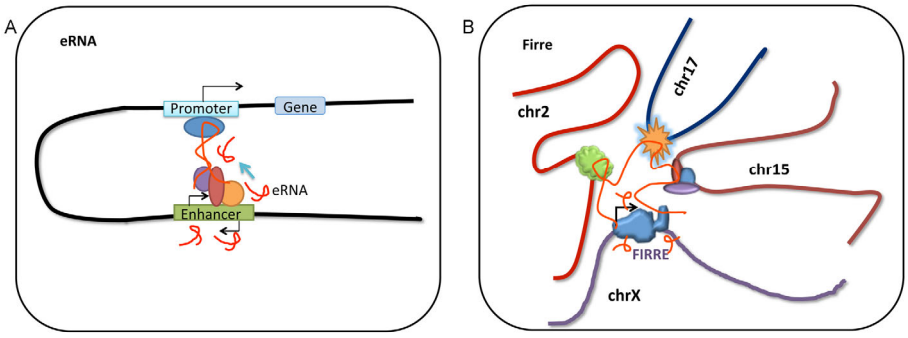

Figure 1 Long noncoding RNAs (lncRNAs) facilitate chromosomal interactions. A, Enhancer-templated non-coding RNAs (eRNAs) are involved in enhancer-promoter interactions. B, Firre forms an inter-chromosomal compartment to co-regulate transcriptional activation.

Inter-chromosomal interactions

Long-range chromosomal interactions occur not only within the same chromosome, but also among a plurality of loci on different chromosomes, which are organized in specific nuclear compartments and regulated by common factors. Recently, the lncRNA Firre (functional intergenic repeating RNA element) has been shown to organize multiple chromosomes to establish a nuclear domain (Hacisuleyman et al., 2014). Firre was initially discovered in a screen of functional lncRNAs during adipogenesis (Sun et al., 2013). It is an X-chromosome transcribed, 5.8-kb lncRNA containing 156-bp repeating sequences that form the secondary structure. Firre interacts with the nuclear matrix factor hnRNPU via its repeating domains, and coats 5-MB chromatin regions of the X chromosome *in cis*. In addition to its *cis*-acting role, Firre also acts *in trans* on loci from at least five different chromosomes, including chromosomes 2, 9, 15, and 17. These sites include many genes related to energy metabolism. Importantly, either the depletion of Firre or the knockdown of hnRNPU leads to a loss of these *trans*-chromosomal interacting loci (Hacisuleyman et al., 2014). These data demonstrated that Firre affects nuclear architecture by mediating inter-chromosomal interactions. Although the case of Firre provided evidence that inter-chromosomal interactions are mediated by lncRNAs, the proposed mechanism needs to be proven by additional investigations of other lncRNAs.

lncRNAs ARE RELATED TO NUCLEAR BODIES

The eukaryotic cell nucleus is compartmentalized to coordinate cellular processes, such as RNA synthesis and processing, DNA replication, and ribosome subunit assembly. Relatively well-characterized nuclear bodies include the nucleolus, nuclear speckle, paraspeckle, PML (promyelocytic leukemia protein) body, Cajal body and etc. These bodies are highly dynamic, and their biological roles are still not fully known. LncRNAs are associated with the function of nuclear bodies, and some (such as Neat1 and IGS) play crucial roles in establishing and maintaining these bodies (Figure 2).

Neat1 and paraspeckles

The paraspeckle is a kind of sub-nuclear structure near the nuclear speckle with a typical size of approximately 0.5 μm, and each cell contains about 10–20 paraspeckles (Fox et al., 2002). It exists in almost all cell types, except for human embryonic stem (ES) cells (Chen and Carmichael, 2009). The main function of the paraspeckle is to retain mRNAs with adenosine to inosine modifications in the nucleus, thereby regulating the expression level of these genes (Fox these mRNAs usually contain Alu elements in humans and type B1 and B2 inverted repeat elements in mice. The key and Lamond, 2010). The 3′ UTRs (untranslated regions) of

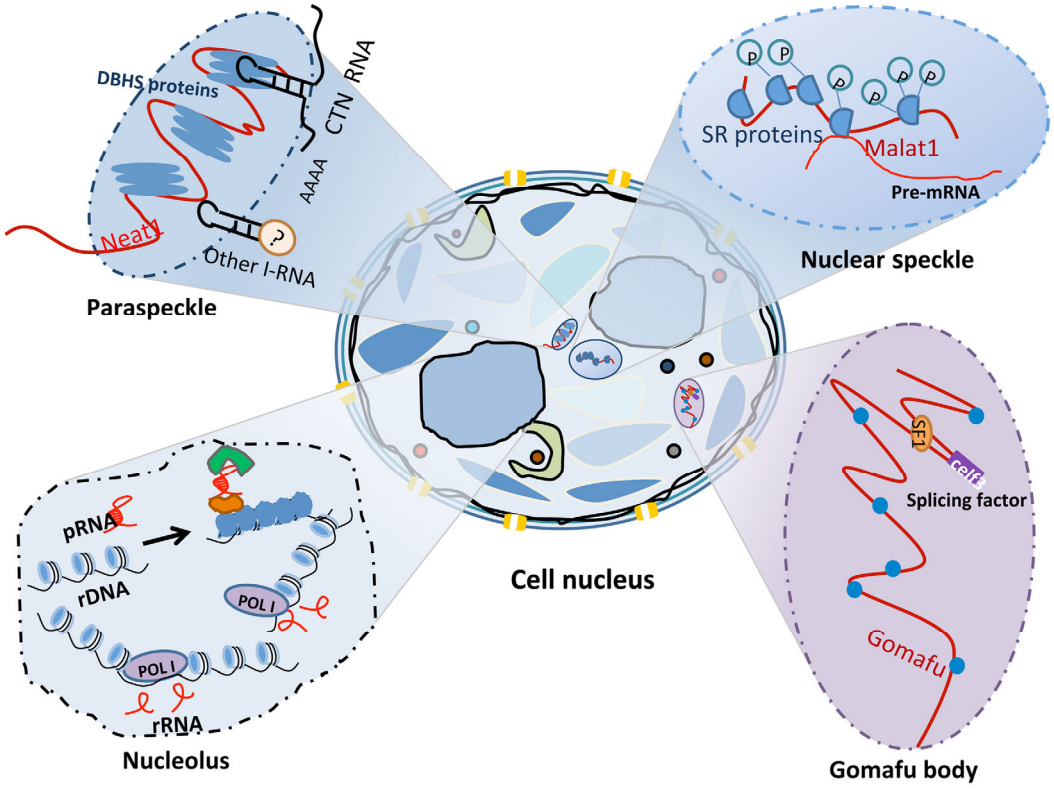

Figure 2 LncRNAs participate in the organization of nuclear bodies. The cartoon represents the landscape of an interphase mammalian cell nucleus. The four well-characterized nuclear bodies described are the paraspeckle, nuclear speckle, Gomafu body, and nucleolus.

components of the paraspeckle include the proteins PSPC1 (paraspeckle protein1), SFPQ (splicing factor, proline- and glutamine-rich), and NONO (non-POU domain-containing octamer-binding protein), which share about 50% sequence identity within two N-terminal RNP-type RNA recognition motifs and a C-terminal coiled-coil domain, and the lncRNA Neat1 (nuclear-enriched abundant transcript 1) (Bond and Fox, 2009).

Neat1 is conserved in mammals and has two isoforms in both humans and mice, Neat1-1 and Neat1-2 (Menε and Menβ in mice), which are 3.7 and 22.7 kb (3.2 and 20.7 kb in mice), respectively (Guru et al., 1997). Treating cells with RNase destroys paraspeckles, which suggests that its structural integrity depends on the presence of specific RNAs (Fox et al., 2005). A number of gain- and loss-of-function studies further demonstrated that Neat1 is essential for the establishment and maintenance of paraspeckles (Clemson et al., 2009; Sasaki et al., 2009; Shevtsov and Dundr, 2011; Sunwoo et al., 2009) via scaffolding core proteins, i.e., NONO, SFPQ, and PSPC1 (Sasaki et al., 2009; Souquere et al., 2010). Interestingly, these processes are dependent on the transcriptional activity of Neat1, as transcription inhibition prevents the establishment of new paraspeckles, even though Neat1 RNA is abundant (Mao et al., 2011).

Unexpectedly, Neat1 knockout mice do not show obvious phenotypes, except for the abolishment of paraspeckles, which suggests that the paraspeckle is nonessential for normal life activities in mice, but is involved in the response to stimuli or stress (Nakagawa et al., 2011). Furthermore, after treatment with a proteasome inhibitor, the size of the paraspeckle increases due to the upregulation of Neat1 transcription (Hirose et al., 2014), and tumor hypoxia induces paraspeckles by activating Neat1 expression (Choudhry et al., 2014), indicating that the paraspeckle is a pressure-responsive nuclear substructure. However, two other investigations have revealed that Neat1 and paraspeckles are required for mammary gland development and lactation (Standaert et al., 2014) and are associated with the early phase of amyotrophic lateral sclerosis (Nishimoto et al., 2013). A recent study reported that the transfection of 20-mer phosphorothioate-modified antisense oligonucleotides can recruit core proteins to form paraspeckle-like foci in the absence of Neat1 RNA (Shen et al., 2014), suggesting a general mechanism of nucleic acid-mediated nuclear body formation.

pRNA and the nucleolus

As the site of ribosomal RNA synthesis and subunit assembly, the nucleolus is probably the most well known nuclear domain. Under specific stimuli, lncRNAs can be induced from large intergenic spacers (IGS) of rDNA clusters, and these IGS lncRNAs act as decoys to retain selected proteins, including VHL, Hsp70, and MDM2/PML, into the nucleolus (Audas et al., 2012).

Interestingly, the IGS lncRNA and its interacting proteins form a large subnucleolar structure named the detention center (DC), and the formation of the DC is dependent on the expression of IGS lncRNA (Jacob et al., 2013). A recent report has revealed that the maturation of pRNA, originated from the processing of an IGS lncRNA, is required for the establishment of heterochromatin at ribosomal RNA genes during ES cell differentiation (Savic et al., 2014). These data suggested that lncRNA regulates the structure and function of the nucleolus under environmental stimuli and during development.

Malat1 and nuclear speckles

The lncRNA Malat1 (metastasis-associated lung adenocarcinoma transcript 1) was originally identified in non-small cell lung cancer cells (Ji et al., 2003). It is transcribed from the human genome at a locus 58 kb downstream of Neat1, known as Neat2 (nuclear enriched abundant transcript 2) (Hutchinson et al., 2007). Similar to Neat1, Malat1 is ubiquitously expressed and is one of the most abundant lncRNAs in the nucleus owing to its stable structure (Hutchinson et al., 2007; Zhang et al., 2012). Furthermore, Malat1 is evolutionarily conserved in vertebrates, especially its 3′ end, with up to 90% similarity between humans and mice (Ulitsky et al., 2011). In humans, the 8.5-kb transcript of Malat1 is processed by various ribonucleases to form a tRNA-like 61-nt small RNA at the 3′ end called mascRNA, which is transported out of the nucleus (Affymetrix and Cold Spring Harbor Laboratory, 2009; Wilusz et al., 2008). The large, 6.7-kb fragment is retained in the nucleus and enriched in nuclear speckles (Hutchinson et al., 2007).

Nuclear speckles are highly dynamic nuclear domains, which are composed of various precursor mRNAs (pre-mRNA) and splicing factors. Studies have shown that Malat1 in nuclear speckles are involved in mRNA modification and splicing by recruiting a variety of pre-mRNA splicing factors to the activation sites (Tripathi et al., 2010). Although Malat1 regulates gene expression in nuclear speckles, it is not essential for the formation or maintenance of nuclear speckles, which is different from Neat1. Down-regulation of Malat1 does not affect the expression or localization of nuclear speckle markers (Hutchinson et al., 2007; Nakagawa et al., 2012; Tripathi et al., 2010). According to some studies, Malat1 reduction can cause a series of phenotypic changes, including apoptosis and cell cycle progression (Tripathi et al., 2010; Tripathi et al., 2013). Surprisingly, three Malat1 knockout studies have shown no obvious phenotypic defects (Eissmann et al., 2012; Nakagawa et al., 2012; Zhang et al., 2012), and the deletion of Malat1 does not have a direct impact on RNA splicing. Only two of these studies have suggested that Malat1 knockout has a slight impact on the expression of adjacent genes, including Neat1. Although Malat1 is a well-studied lncRNA and has broad physiological functions, particularly in tumorigenesis

(Gutschner et al., 2013a; Gutschner et al., 2013b; Ji et al., 2014), the detailed molecular mechanisms underlying these functions have yet to be uncovered.

Gomafu

Another lncRNA related to nuclear domain formation is Gomafu, also known as MIAT (myocardial infarction associated transcript) or RNCR2 (retinal non-coding RNA 2) (Ishii et al., 2006; Sone et al., 2007). Gomafu is a 9-kb lncRNA located in the nucleus, and has more than 10 alternative isoforms. Unlike Neat1 and Malat1, which are expressed ubiquitously, Gomafu is only expressed in some cells of the fetal rat brain and adult nervous system, although it is conserved in amphibians, birds, and mammals (Rapicavoli et al., 2010; Tsuiji et al., 2011).

Gomafu RNA has been detected as discrete dots in the nucleus, which do not colocalize with any known nuclear bodies. Interestingly, the formation and maintenance of this new kind of nuclear domain are not dependent on transcriptional activity, unlike paraspeckles and nuclear speckles (Sone et al., 2007). It has been found that a chicken homolog of Gomafu contains multiple "UACUAAC" tandem repeats, a conserved intron branch sequence in *Saccharomyces cerevisiae*, which bind splicing factor SF1 (splicing factor 1) *in vivo* or *in vitro* (Tsuiji et al., 2011). Although the interaction between Gomafu and SF1 is not necessary for its localization, Gomafu might affect splicing by interactions with splicing factors, similar to Malat1. A recent study confirmed that Gomafu binds the splicing factors QKI (quaking homolog, KH domain RNA binding protein) and SRSF1 (serine/arginine-rich splicing factor 1), and dysregulation of Gomafu leads to inaccurate alternative splicing patterns, which are the same as those observed in schizophrenia (Barry et al., 2014). Although the lncRNA Gomafu may represent a novel model for lncRNA-mediated regulation of nuclear architecture, its molecular mechanisms need further studies.

X-CHROMOSOME INACTIVATION: AN EXAMPLE OF COORDINATED REGULATION OF NUCLEAR ARCHITECTURE BY lncRNAs

In mammals, to balance the expression level of X-linked genes between males and females, one X chromosome in female cells is silenced randomly. X-chromosome inactivation (XCI) is a highly complicated and coordinated process that is controlled by a series of lncRNAs transcribed from the X-inactivation center (Xic), including Xist, Tsix, Jpx, and Ftx (Gendrel and Heard, 2014; Lee, 2012). Briefly, Xist, the key regulator of XCI, coats the entire X-chromosome and recruits polycomb protein complex 2 (PRC2) to induce repressive and condensed chromatin. Then, the inactivated X-chromosome aggregates to a nuclear domain named the Barr body, and is positioned near the nuclear membrane (Figure 3).

An earlier study demonstrated that ectopic expression of Xist in chromosome 12 induces chromosome-wide inactivation (Lee and Jaenisch, 1997). A recent study has shown that inserting inducible XIST to one copy of chromosome 21 (Chr21) in Down's syndrome pluripotent stem cells causes the entire chromosome to be coated and inactivated by XIST (Jiang et al., 2013). These results indicate that Xist is sufficient to initiate the inactivation of its transcribed chromosome. In undifferentiated mouse ES cells, both

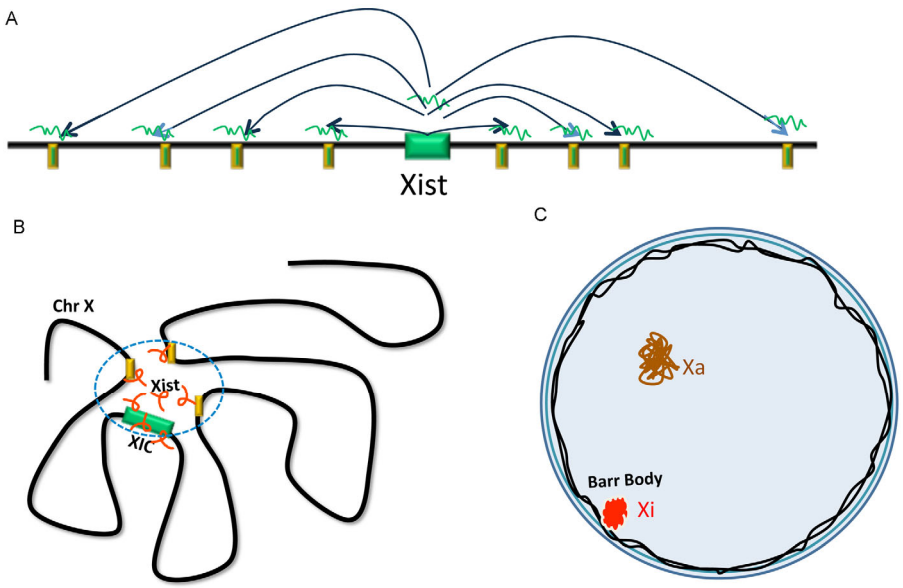

Figure 3 Xist controls X chromosome inactivation by reshaping nuclear architecture. A, Xist is transcribed from the X-inactivation center (green) and spread to the entire chromosome. B, Xist searches for targets based on the 3D chromatin conformation. C, Inactivated X chromosome forms a Barr body and is localized to the nuclear periphery.

X-chromosomes remain active, and the expression of Xist is extremely low. Pluripotent factors, such as Oct4, Nanog, and Rex1 and the lncRNA Tsix inhibit the expression of Xist in ES cells; upon differentiation, Xist is immediately activated and expressed from the future inactive X-chromosome (Gendrel and Heard, 2014). In mouse embryonic development from the 4-cell stage to preimplantation, XCI is imprinted to inactivate the paternal X chromosome. After implantation, both X chromosomes will be reactivated in the cells of the inner cell mass, and, subsequently, one chromosome will be inactivated randomly. Studies have shown that these two XCI processes may rely on different mechanisms, which are not fully understood.

Two recent studies have analyzed chromatin targets of Xist globally using hybridization-based purification (Engreitz et al., 2013; Simon et al., 2013); they showed that Xist identifies its targets by exploiting the 3D conformation of the X chromosome, rather than by searching for specific sequences (Engreitz et al., 2013; Simon et al., 2013). Simon et al. further demonstrated that Xist spreads on the X chromosome following a two-step mechanism: first, to gene-rich islands and then to gene-poor regions. It should be noted that these studies were based on large cell populations and the data are average patterns for millions of cells. A recent paper explored the ultrastructure of the Barr body at the single-cell level, using 3D super-resolution microscopy (Smeets et al., 2014). They found that there are less than 100 distinct Xist RNA foci in a Barr body, which are enriched on the boundaries of collapsed active nuclear compartments, suggesting a non-uniform "coating" of Xist on the inactive X chromosome (Smeets et al., 2014). These controversial results highlight the importance of comparing and integrating data from high-throughput and single-cell assays.

OUTLOOK

In summary, recent advances have demonstrated that some lncRNAs are involved in multiple aspects of nuclear architecture, but the list remains short. Although thousands of lncRNAs have been identified, their functions and underling mechanisms need to be elucidated. One interesting direction is to explore their potential involvement in nuclear architecture under various physiological or pathological conditions. For example, the lncRNA VAD, which belongs to the recently discovered very long intergenic ncRNAs (vlincRNAs) (St Laurent et al., 2013), is required to maintain oncogene-induced senescence (Lazorthes et al., 2015). VAD activates the master gene *INK4 in trans*, presumably by promoting the removal of repressive H2A.Z at this locus (Lazorthes et al., 2015). Additional investigations are needed to detect potential physical *trans* interactions involving VAD.

Furthermore, as the nucleus is highly dynamic, it would be interesting to investigate lncRNAs involved in nuclear dynamics. As an example, the lncRNA TERRA (telomeric repeat-containing RNA) plays critical roles in the maintenance of telomerase activity and homeostasis of chromosome ends (Cusanelli and Chartrand, 2015). Intriguingly, St Laurent et al. proposed a theory that darker matter RNAs (including lncRNAs) act as "intelligent scaffolds" in establishing dynamic and reversible nuclear micro-domains and in differentially binding other macro-molecules to modulate nuclear processes, such as epigenetic signaling (St Laurent et al., 2012). Experimental evidence is needed to evaluate this interesting hypothesis.

However, methodological imperfections are still a major limitation in this field. More reliable and user-friendly techniques need to be developed to detect RNA interactions with DNA/RNA/proteins, the spatial localization of low-abundance RNAs, the structures of lncRNA complexes, etc (Zhang et al., 2015; Zhu et al., 2013). For example, to detect chromatin interactions, conformation capture-based assays (HiC, ChIA-PET, etc.) and hybridization-based methods (such as ChIRP (chromatin isolation by RNA purification) and RAP (RNA antisense purification)) require large numbers of cells. Thus, the results represent the averages of millions of cells, and do not reflect the variability among cells. Currently developed super-resolution microscopy combined with 3D-FISH can be used to detect nuclear architecture at the single cell level, thus providing complementary data to high-throughput assays (Smeets et al., 2014). Moreover, given the general roles of lncRNA as "organizers" (Rinn and Chang, 2012), current strategies, which mainly come from studies of coding genes, need to be improved accordingly (Yin et al., 2015). In light of current studies, lncRNAs could act as general regulators of nuclear architecture, although many mysteries need to be uncovered.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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