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Review

Noncoding RNA-chromatin association: Functions and mechanisms

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ABSTRACT

Pervasive transcription of the mammalian genome produces hundreds of thousands of noncoding RNAs (ncRNAs). Numerous studies have suggested that some of these ncRNAs regulate multiple cellular processes and play important roles in physiological and pathological processes. Notably, a large subset of ncRNAs is enriched on chromatin and participates in regulating gene expression and the dynamics of chromatin structure and status. In this review, we summarize recent advances in the functional study of chromatin-associated ncRNAs and mechanistic insights into how these ncRNAs associate with chromatin. We also discuss the potential future challenges which still need to be overcome in this field.

1. Introduction

More than 98% of the human genome consists of noncoding sequences. It is estimated that more than 75% of the human genome can be transcribed. The pervasive transcription of the human genome produces tens of thousands of RNA transcripts [1]. Over the last few decades, numerous studies have proved that RNAs do not function solely as messengers for passing information from DNA to protein, but play versatile regulatory roles in almost all cellular processes. It is noteworthy that the majority of these regulatory RNAs are ncRNAs. Importantly, functional analyses have revealed that numerous ncRNAs are implicated in cellular processes and have demonstrated relevance to human diseases [2,3].

As the major place where RNAs are synthesized, eukaryotic chromatin is also regulated by these RNAs in turn. As early as the 1980s, researchers found that treating cells with RNase to globally degrade RNAs, or with transcription inhibitors to specifically disrupt chromatin-associated transcribing RNAs, severely impaired nuclear structure detected by microscopy [4,5]. Later studies confirmed these observations at the molecular level [6,7]. While the majority of RNase-degraded, transcription-dependent, nuclear RNAs comprise newly synthesized pre-messenger RNAs (pre-mRNAs), a subset of nuclear ncRNAs has also been identified, and some of them have been proved to participate in the regulation of transcription and chromatin structure (Section 2).

Recently, there have been several excellent reviews that have comprehensively summarized the function of ncRNAs, especially for long noncoding RNAs (lncRNAs) [8,9], as well as the underlying mechanisms governing RNA subcellular localization [10,11]. In this review, we mainly focus on a specific group of ncRNAs—chromatin-associated ncRNAs. We begin by introducing the different classes of chromatin-associated ncRNAs and their functions on chromatin. After that, we summarize recent advances in understanding the mechanisms by which ncRNAs tether to chromatin. Finally, we discuss some potential challenges and unanswered questions that remain in order to gain a deeper understanding of the function and regulation of chromatin-associated ncRNAs.

2. Classification and functions of chromatin-associated ncRNAs

Our understanding of the non-coding RNA world has always been accompanied by the development of relevant technologies. Thanks to high-throughput techniques such as microarray, high-throughput RNA-seq, GRO-seq (global run-on sequencing), TT-seq (transient transcriptome sequencing), which detect stable and transient RNA transcripts [12–14], and cutting-edge techniques such as GRID-seq (global RNA interactions with DNA by deep sequencing), MARGI (mapping RNA-genome interactions), ChAR-seq (chromatin-associated RNA sequencing), RD-SPRITE (RNA & DNA split-pool recognition of interactions by

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Table 1
Comparison of mRNAs with chromatin-associated ncRNAs.

Features	mRNAs	lncRNAs	TSSa / eRNAs	Repeat RNAs	snRNAs and snoRNAs
Expression level	high	moderate	moderate	low	high
Stability	high	moderate	low	low	high
Chromatin enrichment	low	high	high	high	high
Function *in cis* or *in trans* on chromatin	some *in cis*?	mostly *in cis*	*in cis*	mostly *in cis*	*in trans*
Splicing efficiency	efficient	inefficient	mostly unspliced	mostly unspliced	–
Conservation	high	moderate	moderate	low	high
Tissue specificity	moderate	high	high	moderate?	some with specificity
Expressed from	euchromatin	euchromatin	euchromatin	eu- & hetero- chromatin	euchromatin

tag extension), which detect RNA-chromatin interactions [7,15-18], our knowledge of the characteristics of ncRNA binding to chromatin has been greatly broadened. In general, in comparison to messenger RNAs (mRNAs), except some certain types of ncRNAs such as small nuclear RNAs (snRNAs) and small nucleolar RNAs (snoRNAs), most chromatin-associated ncRNAs are less conserved, less processed, expressed at a lower level, but exhibit higher tissue specificity, and are prone to chromatin association and targeting by nuclear surveillance pathways for degradation [19–22]. These features have raised some arguments that most chromatin-associated ncRNAs represent non-functional noise [23]. However, increasing evidence suggests that at least a substantial fraction of chromatin-associated ncRNAs are functional and play vital roles in various physiological and pathological processes, such as early embryonic development [24–26], heart development [27,28], immune responses [29,30], genomic stability [31,32], tumorigenesis [33–35]. In addition, it is becoming increasingly evident that the retention and unstable nature of ncRNAs on chromatin correlate with their function and processing. On the one hand, ncRNAs conduct their molecular function by regulating gene expression and chromatin structure in the nucleus and on chromatin. On the other hand, nuclear retention and degradation of these RNAs prevents the export of noncoding transcripts, as excessive noncoding sequences in the cytosol may swamp the protein synthesis machinery [36]. In this section, we classified chromatin-associated ncRNAs into four groups based on their characteristics and origins (Table 1), and discuss their molecular functions on chromatin.

2.1. Chromatin-associated lncRNAs

LncRNAs are a group of non-protein-coding transcripts with lengths more than 200 nt. It is estimated that the human genome encodes more than 13,000 lncRNAs, although this number may vary across different databases [23]. For example, from the latest collection in the NONCODE database, nearly 100,000 human lncRNAs are identified [37], while a systematic survey of RNA transcripts with accurately defined 5′ ends and expression profiles across human major primary cell types and tissues conducted by FANTOM, suggests that the human genome encodes more than 27,000 lncRNAs [3]. Based on the relative positional relationship between a lncRNA and the nearest gene, lncRNAs can be further classified, and this has been well summarized by previous papers [38,39]. Similar to mRNAs, most lncRNAs are transcribed by RNA polymerase II (RNA Pol II). Furthermore, lncRNAs commonly exhibit a 5′ end capped by 7-methyl guanosine (m7G) and a 3′ end that is polyadenylated, a significant fraction of lncRNAs also contain multiple exons, which are subject to spliced events, albeit with potentially low efficiency [40,41].

It has been realized for a very long time that lncRNAs function in regulating gene expression on chromatin. The most well-known example is *Xist*, which represses the expression of most genes on the X chromosome, where it is expressed, and mediates the dosage compensation in mammals [42]. With the advancement of technologies for the detection and functional perturbation of lncRNAs, more and more lncRNAs were proven to modulate gene expression and chromatin structures on chromatin. Meanwhile, researchers gradually realized that the regulatory effects of lncRNAs on gene expression are more intricate than initially envisaged. In this section, we summarize recent advances in comprehending the role of lncRNAs in regulating gene expression and chromatin structure. We also discuss potential challenges that need to be overcome to decipher the intrinsic principles of lncRNA's function on chromatin.

2.1.1. Chromatin-associated lncRNAs prevalently regulate gene expression in cis

One of the primary roles of chromatin-associated lncRNAs is to modulate gene expression in a *cis*-regulatory manner. This observation is supported by the fact that most lncRNAs are mainly bound proximity to their transcriptional sites [7,16]. It should be mentioned that the *cis*-regulatory effect of a lncRNA is not limited to the immediate vicinity of its transcription site. In some cases, such as for the lncRNAs *Xist* and *roX*2, their transcripts spread along the chromatin for many megabases and may even encompass the entire chromatin from which they are transcribed [43–45].

Initially, several individual cases suggested that some lncRNAs regulate local gene expression through interactions with transcriptional activators or repressors (Fig. 1a). For example, *Khps1*, an antisense lncRNA transcribed from the proto-oncogene *SPHK1*, forms RNA/DNA triplexes (Section 3) with the *SPHK1* promoter, and further recruits the histone acetyltransferase p300/CBP to promote *SPHK1* transcription [46]. Similarly, some lncRNAs facilitate the local activation of *HOX* genes by recruiting chromatin regulators like the MLL (mixed lineage leukemia) complex [47,48].

To determine whether this type of local regulation represent a common mechanism of lncRNA function on chromatin, several studies employing scalable perturbation of lncRNA function have been conducted [39,49,50]. For example, functional analysis of seven intergenic-localized lncRNAs suggests that they function like "enhancers" that promote the expression of nearby genes within 300 kb [49]. Specifically, about 20% of total lncRNAs in humans and mice are transcribed divergently with a paired mRNA, and these divergent lncRNAs are prone to co-localize and co-express with genes encoding transcription factors and developmental regulators [39]. A study showed that functional perturbation of 24 divergent lncRNAs in mouse embryonic stem cells (mESCs), impaired the activation of nearby protein-coding genes in 75% of cases [39]. The authors focused on one lncRNA, *Evx1as*, and proved that it was activated earlier and acted upstream of the divergent protein-coding gene, ensuring proper spatiotemporal expression of the protein-coding gene [21]. The local regulatory effect of divergent lncRNAs was further supported by later studies [27,28,50,51]. Collectively, these studies suggest that lncRNA-mediated transcriptional regulation may represent a general mechanism that is prevalently utilized to fine-tune the spatiotemporal expression of local genes.

2.1.2. Chromatin-associated lncRNAs regulate chromatin interactions

Chromatin-associated lncRNAs also participate in regulating chromatin structures. For example, *Firre* is a lncRNA transcribed from the X chromosome which consists of multiple unique repeating RNA domains (RRDs). These RRDs interact with the nuclear matrix protein HN-

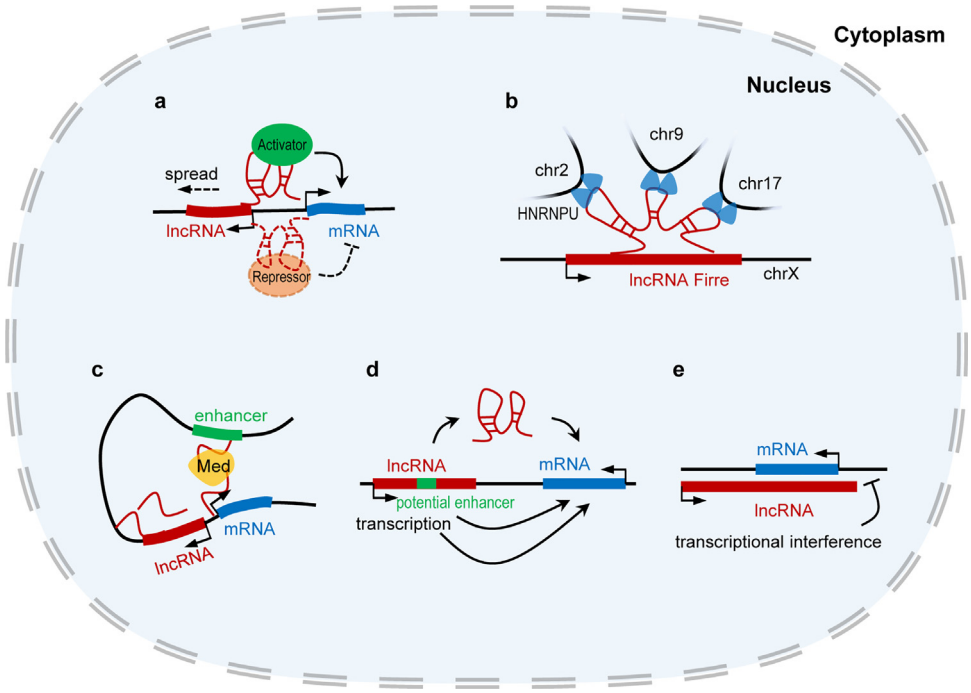

Fig. 1. Representative functions of chromatin-associated lncRNAs on chromatin. (a) LncRNA regulates local gene expression through interaction with transcription activators or repressors. (b) LncRNA *Firre* interacts with HNRNPU and tethers chromosomes 2, 9 and 17 with chromosome X where it is transcribed from. (c) Chromatin-associated lncRNA activates nearby gene expression through interaction with Mediator (Med) complex and promotes enhancer-promoter interaction. (d) Besides RNA transcripts, the genomic DNA encoding the lncRNA and the transcription status of this locus also participate in regulating local gene expression. (e) LncRNA inhibits the expression of a convergently transcribed gene through interference with RNA polymerase II recruitment.

RNPU, and mediate the trans-chromatin interaction between the *Firre* locus and several other loci located in mouse chromosomes 2, 9, 15, and 17 [52] (Fig. 1b).

The functions of lncRNAs in regulating gene expression and chromatin structure are often interdependent. For example, the inactivation of the X chromosome relies on the stepwise alteration of the chromatin structure, which is mainly organized by *Xist* in cooperation with transcription repressors and chromatin structural regulators [43,44,53,54]. In addition, some of the "enhancer-like" lncRNAs mentioned above interact with the mediator component, promoting long-range chromatin interaction between enhancers and promoters that the lncRNA transcripts are associated with. This, in turn, promotes the expression of local target genes [39,55] (Fig. 1c).

In another case, *CCAT-L* is a lncRNA located 515 kb upstream of the oncogene *Myc, CCAT-L* regulates the expression of *Myc* through modulating the interaction between *Myc* promoter and its enhancer, to which *CCAT-L* is associated. *CCAT-L* achieves this regulation through two mechanisms—on the one hand, it interacts with CTCF (CCCTC-binding factor), a key regulator of chromatin organization, which modulates the chromatin confirmation at loop regions formed between the promoter and enhancers [56]. On the other hand, both *CCAT-L* RNA and upstream antisense RNAs (uaRNAs) generated from *Myc* promoter interact with HNRNPK, and these two ncRNAs promote the chromatin looping between the *CCAT-L* associated enhancer and *Myc* promoter through HNRNPK oligomerization [57].

To be noted, lncRNAs do not always increase enhancer-promoter looping. In some scenarios, lncRNAs can disrupt enhancer-promoter interaction, or lncRNA promoter compete with the target gene promoter for enhancers, leading to the repression of target gene expression. For instance, in the aforementioned *Myc* case, another lncRNA, *Pvt1*, located downstream of *Myc*, has a promoter that competes with *MYC* for enhancers located at the gene body region of *Pvt1*, thereby inhibiting *Myc* expression [58]. Given that a large subset of lncRNAs are located adjacent to enhancers, particularly super-enhancers [59,60], the regulation of enhancer-promoter connection by lncRNA may represent a general mechanism by which lncRNA modulates gene expression.

2.1.3. Chromatin-associated lncRNAs function beyond their RNA transcripts

As more lncRNAs are investigated and benefited from the development of perturbation techniques like the CRISPR/Cas system, there is growing confidence that some lncRNAs are indeed functional. However, the regulation of gene expression by lncRNAs appears to be more complex than initially anticipated. This complexity is mainly evident in the fact that lncRNAs may function as a unit, which comprises the RNA transcripts, the genomic lncRNA locus, and the transcriptional status of the locus.

Several pieces of evidence suggest that the lncRNA genomic locus may also participate in the function of lncRNAs (Fig. 1d). A representative case is the functional characterization of the lncRNA *Haunt. Haunt* is located ~40 kb upstream of the *HOXA* gene cluster and regulates *HOXA* gene activation during mESC differentiation. Yin et al. systematically characterized the function of *Haunt* in *HOXA* gene activation using strategies like shRNA-mediated knockdown of lncRNA transcripts, promoter knockout, gene body knockout, promoter replacement, and polyadenylation signal site knock-in to induce premature transcriptional termination of *Haunt* [61]. They found that both *Haunt* RNA transcripts and *Haunt* genomic DNA regulate *HOXA* gene expression, but their effects are opposing. *Haunt* genomic DNA contains enhancer-like elements which promote *HOXA* gene expression, whereas *Haunt* RNAs repress *HOXA* gene activation by attenuating the interaction between *Haunt* genomic DNA and *HOXA* DNA [61,62]. Similar distinct regulatory effects of lncRNA genomic DNA and RNA transcripts were observed in later studies of other lncRNAs like *Pvt1* and *Locked*. [58,63].

In addition, the transcription and processing of some lncRNAs also participate in regulating the expression of nearby genes [50,64] (Fig. 1e). For example, the ~118-kb macro lncRNA *Airn* regulates the expression of *Igf2r* (insulin-like growth factor 2 receptor), a protein-coding

gene which is transcribed ~30 kb downstream of the *Airn* transcription start site in an antisense direction. These two genes are located in an imprinting cluster where *Igf2r* is expressed only from the maternal allele, while the paternal allele of *Igf2r*, together with two other genes, *Slc22a2* and *Slc22a3*, is silenced by the expression of *Airn* [65]. The authors inserted a polyadenylation signal at various positions within the *Airn* gene body to terminate its transcription, they found transcriptional overlap between *Airn* and the *Igf2r* promoter, which impedes RNA polymerase II recruitment, rather than *Airn* transcripts, is required for paternal *Igf2r* silencing [66].

Taken together, lncRNAs may function as a unit comprising both the genomic locus and the transcribed RNA, and they may modulate the expression of local genes via a variety of means, which greatly increases the complexity of lncRNA-mediated regulation of gene expression (Fig. 1d). Notably, like lncRNAs, some coding genes can also modulate local gene expression [39,50]. Nevertheless, it is still unclear what features determine whether an RNA can regulate local gene expression or not. A systematic study aimed at dissecting additional genes with similar functions, as well as a comprehensive and detailed mechanistic investigation, are required in future studies.

2.2. Regulatory element-derived ncRNAs and their function in regulating local gene expression

The transcription of genomic regulatory DNA elements, such as promoters and enhancers, produces a subset of noncoding transcripts known as regulatory element-derived ncRNAs. These ncRNAs, based on where they are derived from, are named eRNAs (enhancer RNAs, derived from enhancers), and TSSa-RNAs (transcription start site-associated RNAs) [12,67,68]. To be noted, unlike lncRNAs mentioned above, these ncRNAs are rarely annotated in lncRNA databases, usually are not stable, unspliced, non-polyadenylated and a propensity to be targeted by nuclear surveillance pathways for degradation [19–21] (Table 1). Notably, their chromatin enrichment is largely dependent on their instability, as depletion of the RNA degradation pathway components leads to cytosolic localization as well as increased stability of these RNAs [19,20,22].

The expression of regulatory element-derived ncRNAs exhibits a strong correlation with the activity status of these elements. Notably, the depletion of some of these ncRNAs through antisense oligos (ASOs) impairs mRNA expression that is regulated by these elements [57,69]. Conversely, tethering of eRNAs upstream of a reporter gene slightly elevate reporter's expression [69,70]. These studies suggest that, like lncRNAs, regulatory element-derived ncRNAs also modulate local gene expression. Additionally, it has been postulated that these RNAs act as a driving force for lncRNA origination [71,72]. Intriguingly, several studies have indicated that lncRNAs situated adjacent to regulatory elements may also regulate the activity of these elements, thus adding another layer of control to gene expression [61,73].

An intriguing question is whether regulatory element-derived ncRNAs require specific features to perform their proper function, or whether their RNA property, regardless of the sequence composition, is sufficient for their regulatory function. Clues may come from RNA tethering experiments mentioned above, which have demonstrated that only a subset of eRNAs can elevate reporter gene expression [39,69,70], indicating that functional eRNAs indeed harbor some unique features. In addition, eRNAs have been reported to facilitate the release of NELF (negative elongation factor), a complex that negatively regulates transcription elongation by RNA Pol II, to promote the pause-release of RNA Pol II [74]. A recent study dissecting the sequence and structural features of eRNAs and their relationship with the detachment of NELF has suggested that an RNA length over 200 nt and the existence of several unpaired guanosines are required for eRNA function [75]. Given that these features are present in numerous RNAs, they may represent a general requirement for NELF detachment. It should be noted that a previous study in flies and two recent studies in mammalian cells have suggested that different enhancers may prefer specific promoters [76–78]. These observations imply that ncRNAs generated from different regulatory elements may harbor distinct features and may require specific conditions for their proper functioning. In support of this concept, a recent study identified a functional motif embedded in estrogen-regulated eRNAs that is required for their regulatory function in modulating gene expression [79].

Another intriguing question is how regulatory element-derived ncRNAs exert their local regulatory function on chromatin. Numerous studies have suggested that these ncRNAs can interact with some transcriptional regulators, and regulate local gene expression through recruitment, blocking, or scaffolding of these factors [18,67]. It is worthwhile noting that some transcriptional pioneering factors, like YY1 and CBP/P300, interact with regulatory element-derived ncRNAs and this interaction is required for their proper function [80–82] (Fig. 2a). In addition, several RNA-binding proteins (RBPs) have been proven to function in regulating gene transcription on chromatin [82–84]. For example, WDR43 is an RBP that is critical for ribosome biogenesis. Intriguingly, WDR43 also binds to thousands of TSSa RNAs, eRNAs, and nascent noncoding transcripts, enabling WDR43 to target active promoters and enhancers in mESCs. By modulating the release of P-TEFb, WDR43 regulates the pause-release of RNA Pol II and controls global transcription [84]. Recently, a study has suggested that most chromatin-enriched proteins are indeed RBPs [85]. Upon inspection of their amino acid sequences, most of these chromatin-enriched RBPs are found to contain a high content of low-complexity sequences (LCSs), which have been suggested to potentially promote phase separation, a process involving interactions between multivalent macromolecules and playing an important role in various cellular processes [85,86]. In line with this, recent studies have proposed that chromatin-associated ncRNAs, RBPs, and some transcriptional factors work in concert to modulate gene transcription by controlling the formation and dissolution of transcription-related phase-separated condensates [85,87] (Fig. 2a).

2.3. Repeat-derived ncRNAs

It is estimated that 45–50% of the human genome consists of repetitive sequences. These sequences are predominantly derived from transposon elements (TEs). Based on their origin and sequence features, the repetitive sequences can be classified into LINEs (long interspersed elements), SINEs (short interspersed elements), LTRs (long terminal repeats), satellites, simple repeats, and others [88]. Although for most cells the majority of the repetitive elements are silenced or transcribed at a low level, some repeat elements are specifically expressed in certain cell types or at particular stages of development [89,90]. For example, during embryogenesis, a subfamily of LTR repeats named MERVL is specifically expressed in two-cell-stage embryos and a small proportion of mouse embryonic stem cells (mESCs) [91,92]. A growing body of evidence suggests that a substantial fraction of repeat-derived ncRNAs are mainly retained on chromatin and play important roles in modulating gene expression, chromatin status and structure there.

2.3.1. Repeat-derived ncRNAs regulate gene expression on chromatin

Some repeat-derived ncRNAs regulate gene expression through interacting with transcriptional regulators. For example, in human ESCs, a family of LTR repeats named HERVH (Human endogenous retrovirus subfamily H) generates nuclear-retained transcripts that function as lncRNAs. HERVH RNAs associate with pluripotency gene OCT4 and other transcriptional regulators, promoting the expression of neighboring genes and facilitating pluripotency maintenance of ESCs [93].

In another example, SINE B2 is a group of chromatin-associated short ncRNAs transcribed by RNA polymerase III. Upon heat shock, SINE B2 RNA abundance increases, leading to its interaction with RNA Pol II and subsequent repression of the transcription of specific mRNA genes [94]. Intriguingly, during heat shock, the PRC2 (Polycomb repressive complex 2) component EZH2 also interacts with and catalyzes the cleav-

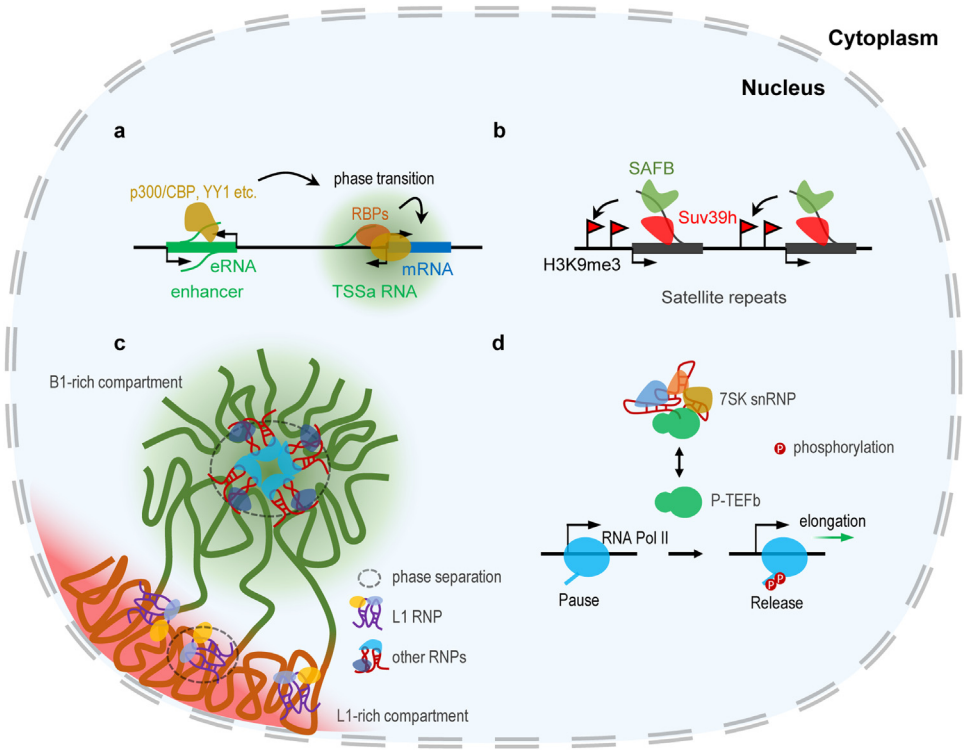

Fig. 2. Representative functions of regulatory element-derived ncRNAs, repeat-derived ncRNAs and 7SK snRNAs on chromatin. (a) eRNA and TSSa-RNA promote local gene expression through interaction with transcription factors and RNA-binding proteins. (b) Satellite repeat-derived ncRNAs facilitate the establishment and maintenance of heterochromatin through interaction with SUV39h and SAFB. (c) L1 and B1 repeats compartmentalize the 3D genome through homotypic clustering and phase separation mechanisms. (d) 7SK snRNP regulates pause-release of RNA Pol II through controlling the release of P-TEFb.

age of B2 RNA, relieving the transcriptional suppression of stress genes [95]. Moreover, during stress, the abundance of another Pol III transcribed repeat-derived ncRNA, SINE B1 (also known as Alu in humans), increases and has been reported to participate in regulating gene expression transcriptionally and post-transcriptionally [96].

Furthermore, it should be noted that the DNA sequence of repetitive elements also plays a regulatory role in gene expression by providing binding sites for certain transcriptional regulators [97]. Given that repeat elements are widely distributed and harbor hundreds to thousands of copies across the genome, they have the potential to regulate a large group of genes and exert a significant impact on global gene expression and cellular status.

2.3.2. *Repeat-derived ncRNAs facilitate heterochromatin formation*

The chromatin of eukaryotes is well organized and can be classified as euchromatin and heterochromatin. The euchromatin is loosely packed and is composed of actively transcribed genes. Heterochromatin, on the other hand, is tightly packed and has low transcriptional activity for most of the time. In mammals, heterochromatin is predominantly composed of certain sets of repeat elements like LINEs, satellites, LTRs. Intriguingly, numerous studies have shown that heterochromatin is not continuously silenced but can be transcribed at a low level or during certain stages. The transcription of heterochromatin is proven to be required for the establishment or maintenance of heterochromatin status. For example, in *Drosophila*, a group of actively-transcribed repeat RNAs named *gypsy*, which originate from heterochromatin, can be processed by DICER, an endoribonuclease which plays a critical role in the RNA interference (RNAi) pathway, to help maintain the pericentromeric heterochromatin [98]. Similarly, in mammals, the formation of pericentromeric heterochromatin is primarily regulated by satellite repeats. The transcription of major satellite repeat RNAs stabilizes heterochromatin architecture by retaining the H3K9me3 methyltransferase SUV39H and the nuclear matrix protein SAFB [99,100] (Fig. 2b).

In addition, a family of repeat-derived ncRNAs named IAPs (intracisternal A particle) regulates certain mammalian heterochromatin regions. IAP RNAs promote heterochromatin through recruiting H3K9me3-related methyltransferases and cofactors in an RNA m^6A (N6-methyladenosine)-dependent manner [101–103]. Notably, several regulators associated with heterochromatin were reported to interact with RNA or RBPs [100,101,103-105], and it was reported that H3K9me3-marked heterochromatin is enriched with numerous RBPs [106]. This suggests that repeat element-derived RNAs may have a general function in heterochromatin regulation.

2.3.3. *Repeat-derived ncRNAs regulate chromatin compartmentalization*

The advent of techniques for detecting chromatin structure, like HiC, ChIA-PET, has revealed that the eukaryotic genome is highly organized, with topologically associating domains (TADs) representing regions of intra-chromosomal interactions [107,108]. Based on their chromatin structure and transcriptional activity, similar TADs tend to associate with each other, resulting in the division of chromosomes into two types of compartments—A and B compartments. A compartments are characterized by active chromatin, while B compartments consist of inactive chromatin [109]. Notably, two types of repeat elements, SINE B1 and LINE1, are enriched in A and B compartments, respectively, demarcating the genome into grossly exclusive domains that are conserved across different cell types and species [90,110].

Both B1 and LINE1 RNAs are enriched in the nucleus and associated with chromatin. Studies have shown that depletion of LINE1 transcripts impairs the A/B compartmentalization, suggesting a regulatory role of LINE1 RNA in chromatin compartmentalization [110]. It has been proposed that the homotypic clustering of repetitive sequences, together with a phase separation mechanism, may promote the compartmentalization of the genome [110] (Fig. 2c). The role of LINE1 in regulating chromatin organization is supported by several other studies. For example, it has been reported that C0t-1 RNAs, which mainly consist of

LINE1 RNAs, are required for the maintenance of proper supercoiled chromatin structure by regulating the oligomerization of HNRNPU (also named SAF-A) [111]. In addition, it has been reported that heterochromatin, where LINE1 repeats mainly localized, is the main driving force for compartmentalization of nuclei [112]. Although further mechanistic investigations are needed to fully understand the underlying mechanisms, these studies collectively suggest that repetitive sequences and their transcripts play a crucial role in shaping the architecture of our genome.

2.4. Chromatin-associated snRNAs and snoRNAs

In addition to ncRNAs mentioned above, it has been suggested that certain types of short, abundant ncRNAs also exhibit association with chromatin. These ncRNAs are usually containing fewer than 200 nucleotides. It is worth noting that this category also includes ncRNAs with a length range from 20 to 34 nucleotides like small interfering RNAs (siRNAs), PIWI-interacting RNAs (piRNAs), their functions on chromatin have been well summarized [113,114] and we'll not discuss here.

The most abundant chromatin-associated short ncRNAs are snRNAs and snoRNAs. While snRNAs primarily function in the regulation of pre-mRNA transcription and processing, snoRNAs mainly guide the chemical modifications of other RNAs, such as rRNA, tRNA and other RNAs [115]. Compared to the other three categories of chromatin-associated ncRNA that primarily function *in cis*, it is noteworthy that these chromatin-associated short ncRNAs have longer half-lives, greater mobility, and predominantly exert their function *in trans* (Table 1).

2.4.1. Chromatin-associated snRNAs regulate transcription and RNA processing

The chromatin-associated snRNAs mainly function in modulating the transcription, splicing and 3′end processing of pre-mRNAs. For instance, 7SK snRNA, which is abundant in metazoans, acts as a scaffold and forms a small ribonucleoproteins (snRNP) with transcription-related factors HEXIM1, LARP7, MEPCE and positive transcription elongation factor P-TEFb (a complex formed by Cdk9 and Cyclin T1). The main function of 7SK snRNP is to control the release of P-TEFb, which regulates the pause-release phase transition of transcription (Fig. 2d). Consistent with this, 7SK prevalently binds to gene promoters, and depletion of 7SK leads to a Pol II pause-release defect [116]. Furthermore, 7SK also binds to gene enhancers and regulates the activation of enhancers, a process that can also control the release of paused Pol II [116,117].

The splicing of eukaryotes is performed by spliceosomes, which predominantly comprise five uridine-rich snRNAs that form snRNP complexes, namely U1, U2, U4, U5, and U6 snRNPs [118]. It is suggested that all five of these splicing-related snRNAs are enriched on chromatin [119], and at least the chromatin occupancy regions of U1 and U2 snRNAs have been profiled by genome-wide RNA-chromatin interaction strategies like RNA antisense purification (RAP) or GRID-seq [16,120]. Apart from their canonical function in regulating splicing, which has been well reviewed, U1 and U2 snRNPs also participate in other transcription and RNA processing processes. For example, U1 snRNP plays a crucial role in preventing premature transcription termination through inhibiting cryptic polyadenylation signals (PASs) embedded in the gene body, a process named telescripting [121,122]. Moreover, our recent study has also demonstrated its critical role in promoting ncRNA-chromatin association (see also Section 3.3 below) [22], and U2 snRNP has also been reported to facilitate transcription termination of histone genes and be required for an efficient release of paused Pol II [123,124].

2.4.2. Chromatin-associated snoRNAs regulate RNA processing, chromatin structure, and genome stability

The majority of snoRNAs are predominantly located in nucleolus, where they guide the post-transcriptional modifications of rRNAs [115]. However, a subset of snoRNAs is also found in other subnuclear regions, and it has been demonstrated that they associate with chromatin there, especially in *Drosophila* [15-17,125]. The function of these chromatin-associated snoRNAs are diverse. For instance, in *Drosophila*, the class of chromatin-associated RNA is largely composed of snoRNAs, which interacts with Df31 and is required for maintaining an open chromatin structure in euchromatic regions [125]. Although the chromatin association of snoRNA is not so prevalent in mammalian cells as in *Drosophila*, some specific snoRNAs exhibit high chromatin enrichment and participate in crucial cellular processes like genome stability maintenance and RNA processing. In particular, a subgroup of snoRNAs that lack modification targets, named as orphan snoRNAs, exhibits dynamic chromatin association in response to DNA damage stress, and contribute to regulating genome stability and the differentiation of malignant myeloid cells [126]. Additionally, a subset of snoRNAs associates with 3′ processing complex and regulates mRNA 3′ processing on chromatin [127]. Given the high abundance and significant sequence diversity of snoRNAs, they are likely to play multifaceted roles on chromatin which are yet to be fully explored.

3. Mechanisms of ncRNA-chromatin association

As mentioned above, systematic surveys investigating RNA-chromatin association patterns has suggested that mature mRNAs are depleted from chromatin, while most ncRNAs are enriched within the three-dimensional proximity of their transcriptional loci [7,16]. This observation raises the question why do ncRNAs exhibit a propensity for chromatin retention, and how do they associate with chromatin? Several recent studies probing the mechanism of ncRNA-chromatin association may provide some insight into potential explanations for this phenomenon [19,22,128,129]. In this section, we summarize three primary mechanisms that govern ncRNA-chromatin tethering, and try to offer some insights into the underlying reasons for the preference of ncRNAs for association with chromatin.

3.1. Direct RNA-DNA interaction

Some chromatin-associated ncRNAs have been observed associate directly with DNA via certain sequence features or during particular stages of RNA synthesis. This association is mainly mediated by two mechanisms: R-loops or RNA:DNA triplexes. Both R-loops and RNA:DNA triplexes consist of a single-stranded RNA and two complementary DNA strands. However, a key distinction between the two is that in an R-loop, the RNA strand hybridizes with one of the DNA strands and leaves the other one unpaired, while in an RNA:DNA triplex, the RNA molecule inserts into the major groove of the paired DNA strands [130,131] (Fig. 3a and b).

3.1.1. R-loops

It is proposed that the major way of retaining nascent RNA on chromatin is via an R-loop, which entails annealing the nascent RNA back to the template DNA [18]. However, such R-loop is thought to be a threat to genomic integrity and epigenomic stability, therefore it should be stringently and dynamically regulated [132]. Notably, genome-wide mapping of R-loops suggests that they are enriched in active regulatory regions like promoters and enhancers, and associated with GC-skewed sequences, and a free RNA end is required for R-loop formation [133,134]. R-loops may facilitate the tethering of these ncRNAs to chromatin, vice versa, as most transcripts derived from regulatory elements are short-lived [67], the rapid turnover of these RNAs may facilitate the rapid dynamics of R-loops. In support of this idea, depletion of RNA exosomes leads to artificial stabilization of regulatory element-derived ncRNAs, promoting the formation of R-loops and impairing the genomic integrity [20].

In addition to regulatory regions, it has been reported that R-loops can also be formed in some repetitive element regions across different

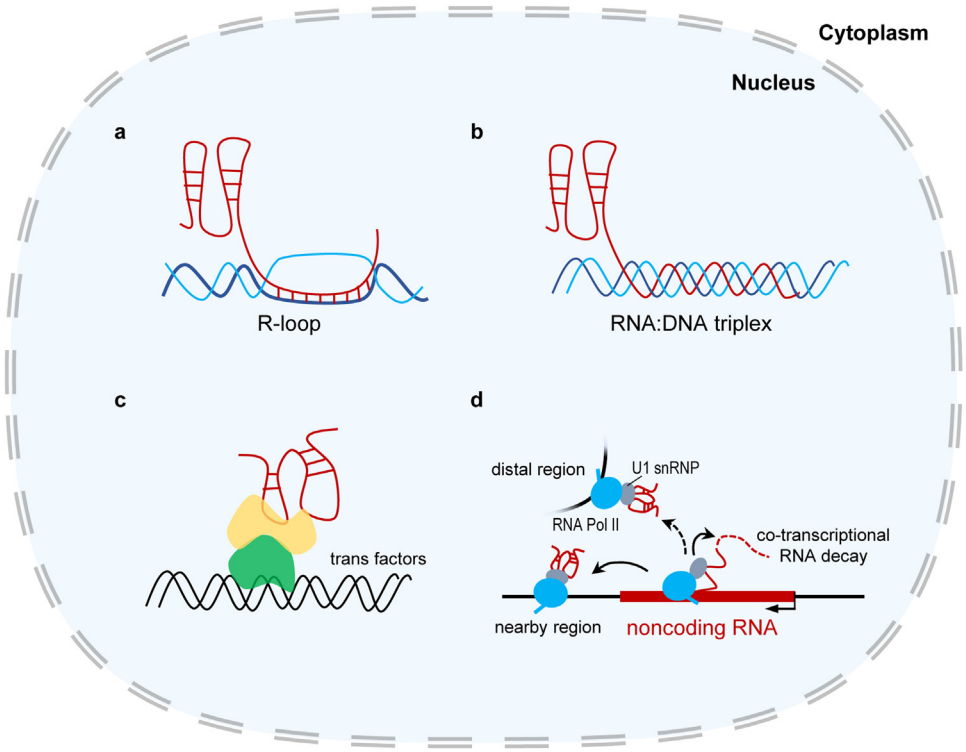

Fig. 3. Representative mechanisms regulating ncRNA-chromatin tethering. (a) NcRNA directly tethers to chromatin by forming an R-loop structure in which one part of the ncRNA strand hybridizes with one strand of the double-stranded DNA. (b) NcRNA directly tethers to chromatin by forming an RNA:DNA triplex structure in which one part of the RNA strand inserts into the major groove of the paired DNA strands. (c) NcRNA indirectly tethers to chromatin through interaction with chromatin-bound *trans* factors. (d) U1 snRNP promotes ncRNA chromatin retention and targeting to nearby or distal regions through interaction with transcriptionally engaged RNA Pol II. This may promote co-transcriptional RNA decay.

species [135,136]. For example, the major satellite repeat RNAs mentioned above associate with the peri-centromere region mainly through forming R-loops. Overexpression of satellite RNAs artificially promotes R-loop formation and DNA damage in the centromere region [100,137]. A recent study has also suggested that *TERRA*, a lncRNA that regulates telomeric chromatin structure, targets chromosome ends through R-loop formation [138]. However, possibly because stable R-loops pose a threat to genomic stability, only a few studies have reported this mechanism of lncRNA-chromatin association.

3.1.2. *RNA:DNA triplexes*

Some lncRNAs utilize RNA:DNA triplex structures for their chromatin tethering. For example, the lncRNA *Khps1* mentioned above targets the promoter of *SPHK1* through an RNA-DNA triplex structure [46]. Additionally, noncoding transcripts transcribed upstream of the *DHFR* promoter and inhibit *DHFR* expression through formation of a stable RNA:DNA triplex at the promoter [139]. RNA:DNA triplex structures also enable ncRNAs to tether to the distal *trans*-chromatin region. For example, the lncRNA *Meg3* targets thousands of regions in the genome by forming RNA:DNA triplexes [140], and it is proposed that the lncRNA *HOTAIR* may use a similar mechanism for chromatin targeting [45]. In addition, two recent studies have suggested that the chromatin association of two functional lncRNAs, *CCTT* and *Kcnq1ot1*, occurs through an RNA:DNA triplex mechanism [141,142]. Notably, the formation of an RNA:DNA triplex requires specific sequence features, usually GA-rich homopurine sequences, enabling the prediction of potential regions that form RNA:DNA triplexes to some extent [143]. However, due to the lack of efficient techniques to directly capture RNA:DNA triplexes, further investigations are needed to identify the genome-wide distribution of these structures and the RNAs that utilize them for chromatin tethering.

3.2. Trans *factors*

As discussed in Section 2, most chromatin-associated ncRNAs fulfill their regulatory role through interaction with RBPs, chromatin regulators and other factors. These regulators also promote the chromatin association of ncRNAs. Thus, for these ncRNAs, functional coupling with chromatin is achieved via indirect interaction (Fig. 3c). An archetypal example is the chromatin tethering of the lncRNA *Xist*. *Xist* comprises six interspersed repeats (A-F) that interact with different proteins. Repeats A, B, E were reported to promote the chromatin association of *Xist* RNA. The A-repeat, which directly interacts with SPEN, is required for *Xist*-mediated X-chromosome inactivation (XCI) and also promotes retention of *Xist* on chromatin [22,43,144-146]. The B-repeat consists of multiple C-rich motifs that interact with HNRNPK and further associate with polycomb proteins to ensure correct spreading of *Xist* RNA along the X chromosome [147–149]. The E-repeat interacts with the nuclear matrix protein CIZ1 (CDKN1-interacting zinc finger protein) and the RBPs PTBP1, MATR3, TDP-43 and CELF. These proteins tether *Xist* RNA to the X chromosome and anchor it to the inactive X (X_i) territory through a phase-separation mechanism [150–152]. Notably, all these repeats, along with their interacting protein partners, are required for proper X chromosome inactivation. These observations suggest that *Xist* RNAs provide a multivalent platform for the assembly of all these factors, which further work in concert with each other to ensure proper X chromosome tethering and XCI. Moreover, these regulators also interact with thousands of other RNAs besides *Xist*, and they may also play a role in the chromatin retention of other noncoding transcripts.

3.3. *Co-transcriptional RNA processing and U1 snRNP*

The processing of RNAs is coupled with transcription, whereas the processing of ncRNAs is proposed to be linked with their function

[153,154]. For most ncRNAs, their chromatin association is also dependent on transcription. Transcription promotes ncRNA chromatin association in two scenarios. Firstly, the chromatin association of some ncRNAs, including stable ones such as *Malat1* and *Neat1*, is dependent on the RNA processing-related factors they interact with. Both *Malat1* and *Neat1* dynamically associate with chromatin, coupled with co-transcriptional RNA processing [22,155-157]. Transcription inhibition impairs their proper localization as well as their chromatin association [22,120,158]. Notably, other stable lncRNAs such as *Xist*, are stably associated with chromatin independent of transcription.

Secondly, the chromatin association of some short-lived ncRNAs is correlated with the way they are synthesized and processed. For example, for some lncRNAs and unstable transcripts, co-transcriptional RNA decay on chromatin results in experimentally observed chromatin enrichment of their transcripts [19,22]. Some transcription regulators like PAF1 and SPT6, modulate the transcriptional activity of ncRNAs, thereby regulating their nuclear retention and chromatin association [159,160]. Collectively, these findings imply that the localization and fate of some ncRNAs are determined even before they are fully transcribed.

U1 snRNP is the most abundant snRNP in eukaryotic cells. As mentioned above, U1 snRNP participate in multiple non-canonical functions on chromatin beyond its canonical function in coordinating pre-mRNA splicing. A recent study has suggested that compared to mRNAs, U1 recognition motifs and U1 binding are highly enriched in ncRNA transcripts, and U1 snRNP plays a pivotal role in promoting the chromatin association of ncRNAs [22]. U1 snRNP promotes ncRNA-chromatin retention co-transcriptionally, coupled with the processing and degradation of ncRNAs: On the one hand, U1 snRNP tethers its interacting ncRNAs to chromatin through interaction with transcriptionally engaged RNA Pol II; on the other hand, U1 snRNP promotes the decay of its tethered RNA on chromatin through cooperation with the downstream polyadenylation signal, lead to an experimentally observed chromatin enrichment of these ncRNAs [22,161,162] (Fig. 3d).

Notably, U1 snRNP accounts for the chromatin retention of a large proportion of ncRNAs, as depletion of U1 snRNP severely impairs the chromatin retention of nearly half of lncRNAs and regulatory element-associated ncRNAs expressed in mESC. Considering the fact that ncRNAs generally harbor a higher content of U1 recognition motifs and stronger U1 binding than mature mRNAs, the U1 snRNP-ncRNA interaction may partially explain why most ncRNAs tend to be retained on chromatin. In addition, U1 snRNP promotes the degradation of these chromatin-tethered ncRNAs, which may partially explain why some chromatin-associated ncRNAs are short-lived [19–22]. Moreover, the interaction between U1 snRNP and transcriptionally engaged RNA pol II provides a driving force to target the U1 snRNP-tethered ncRNA to a nearby or distal region, and facilitate ncRNAs' regulatory function on chromatin.

4. Perspective

In summary, chromatin-associated ncRNAs play important roles in modulating gene expression, chromatin structure and chromatin status in the nucleus. This regulation occurs primarily through interaction with transcription and chromatin regulators, and/or interference with the transcription of target genes. An increasing number of chromatin-associated ncRNAs have been proven to be functional and to regulate gene expression on chromatin through various mechanisms. However, the fundamental principle governing the regulatory role of chromatin-associated ncRNAs in gene expression is still fuzzy. Based on recent genome-wide RNA-chromatin interaction profiling [7,16], the chromatin is crowded with a diverse array of RNAs, most of them are nascent RNAs. Most ncRNA-interacting regulators also interact with these RNAs. Therefore, in the future, some intriguing questions remain to be answered about the roles of these other RNAs and what makes ncRNAs special.

The chromatin tethering of ncRNAs is mainly through direct RNA-DNA interaction or through interaction with other chromatin-bound factors. For most short-lived ncRNAs, co-transcriptional RNA processing, especially RNA decay, contributes to their experimentally observed chromatin enrichment. Although a number of factors are reportedly required for proper chromatin tethering of ncRNAs, most of these factors facilitate but do not determine the tethering. The most representative example is *Xist.* Multiple *cis*-elements and *trans*-regulators function synergistically together to safeguard the proper chromatin tethering and spreading of *Xist*. It should be noted that the interaction between *cis*-elements and *trans*-regulators is often, but not exclusively, required for both the function and chromatin tethering of ncRNA. For example, the *Xist* A-repeat and its interactor SPEN are required for both the repressive function and chromatin tethering of *Xist* [22,144-146], while for E-repeat and its trans interactors, the interaction mainly participated in the chromatin tethering of *Xist* [150–152].

Despite numerous functional ncRNAs being reported, our understanding of the intrinsic principles underlying ncRNA function remains limited. This is partly due to the small number of thoroughly studied ncRNAs, particularly those that have been probed for their key functional domains or structures. It is thought that functional ncRNAs may harbor evolutionarily conserved sequence motifs or structural domains [8]. While digging for more functional ncRNAs, it will be worthwhile to classify them and systematically investigate the sequence and structural features embedded in ncRNA transcripts. Since most ncRNAs are functionally linked to how they are synthesized and processed, and work together with other regulatory mechanisms on chromatin, it is crucial to integrate multiple mechanisms to systematically study and rationally evaluate the function of ncRNAs.

Declaration of competing interests

The authors declare that they have no conflicts of interest in this work.

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