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SINE-derived short noncoding RNAs: their evolutionary origins, molecular mechanisms, and physiological significance

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Short Interspersed Elements (*SINE*s) comprise a significant portion of the genomes of higher eukaryotes, including humans and mice. This review focuses on *SINE*-derived noncoding RNAs (ncRNAs), particularly *BC1*, *BC200*, and *4.5SH* RNA, which are expressed abundantly and in a species-specific manner. These ncRNAs seem to have independently evolved their functions during evolutionary processes: *BC1* and *BC200* have become cytoplasmic translation inhibitors, while *4.5SH* RNA has developed into a nuclear ncRNA that regulates splicing. This review delves into the unique roles of these ncRNAs, with a special emphasis on the recently discovered splicing regulation function of *4.5SH* RNA. Furthermore, we discuss their evolutionary trajectories and potential implications for understanding the complexities of gene regulation.

KEYWORDS

SINE, ncRNA, *BC1*, *BC200*, *4.5SH RNA*, translation, splicing

Introduction

SINEs (Short Interspersed Elements) (Singer, 1982) are among the most "successful" retroelements within mammalian genomes, judging by copy number, reaching up to 1.9×10^6 and 1.6×10^6 copies in humans and mice, respectively (Smit, 1996). In both primates and rodents, two major classes of *SINE*s, *SINE B1*s (or the *Alu* family in humans) and *SINE B2*s, have evolved from distinct, abundant, ribosome-associated noncoding RNAs (ncRNAs): *7SL* and *tRNA*s, respectively (Okada, 1991; Deininger, 2011; Kramerov and Vassetzky, 2011). *SINE*s are thought to amplify themselves non-autonomously, utilizing the reverse transcriptase of autonomous retroelements, known as *LINE*s (Long Interspersed Elements) (Singer, 1982), via a mechanism called target-primed reverse transcription (Deininger, 2011; Kramerov and Vassetzky, 2011). Retro-transposition of *SINE*s can be potentially hazardous to host genomes if inserted into coding sequences or regulatory elements. Furthermore, *SINE* insertions can introduce deleterious exons by providing consensus splice sites inherent to certain *SINE* groups (Sela et al., 2007; Sorek, 2007). Indeed, *SINE* insertions, particularly *Alu* elements, have been implicated in a range of human genetic disorders, including Fukuyama-type muscular dystrophy (Taniguchi-Ikeda et al., 2011), neurofibromatosis type 1 (Wallace et al., 1991), among others. Consequently, the activity of *SINE*s, along with other transposing elements, must be strictly regulated to maintain genomic integrity. In higher eukaryotes, including humans and mice, small RNAs known as piRNAs, processed from precursor ncRNAs containing retroelements, help keep the SINE expression under control. These piRNAs are loaded onto piwi-family proteins,

introducing repressive epigenetic modifications to retroelements, including SINEs, through their association with chromatin modification complexes (Onishi et al., 2021; Wang and Lin, 2021). As such, the expression of SINEs is typically kept at an extremely low level, if any expression occurs at all.

Despite the global repression of SINEs, SINE-related short ncRNAs, distinct from the ancestral 7SL or tRNAs, are abundantly expressed in a species-specific manner (Figure 1A). The small rodent-specific 4.5SH RNA is one of the earliest examples of such species-specific short ncRNA, with its sequence being determined almost simultaneously with the determination of the Alu-element sequence, the firstly discovered SINE (Harada and Kato, 1980; Rubin et al., 1980). The sequence of 4.5SH RNA is highly homologous to a variant of SINE B1 known as pB1d10, suggesting that this could be a direct precursor of 4.5SH RNA (Gogolevskaya et al., 2005). BC1 and BC200, identified as abundant, brain-specific, cytoplasmic RNAs in rats and primates respectively, are other examples of such SINE-related ncRNAs (Sutcliffe et al., 1984; Martignetti and Brosius, 1993; Tiedge et al., 1993). Although they are thought to be functional counterparts, BC1 exhibits homology to Identifier (ID) elements, a tRNA-derived SINE (Sutcliffe et al., 1982), while BC200 originates from a distinct group of SINEs, the Alu family retrotransposon (Figure 1A). These highly expressed SINE-related endogenous ncRNAs are transcribed by RNA polymerase III, similar to ancestral SINEs, but lack an A-rich tail required for retrotranspositions (Kramerov and Vassetzky, 2011). Hence, they are located at a single region in each genome. While BC1 and BC200 are single copy genes (DeChiara and Brosius, 1987; Martignetti and Brosius, 1993), 4.5SH genes are tandemly arrayed at a distinct region

in the genome, chromosome 6 in the case of mice (Schoeniger and Jelinek, 1986). The tandem organization of 4.5SH is reminiscent of the tandemly repeated ribosomal RNA (rRNA) genes, which are generated via unequal crossover during meiosis (Eickbush and Eickbush, 2007).

Even though these ncRNAs were discovered as early as the 1970-80s, their precise molecular functions and physiological roles have only become clearer in the last decade. In this short review, we will summarize the origins, mechanisms of action, and physiological roles of these abundant SINE-derived ncRNAs.

BC1 RNA: rodent-specific short RNA function as a translational regulator in dendrites

The brain cytoplasmic 1 (BC1) RNA was initially identified through cross-hybridization of multiple cDNA clones with a short, ncRNA specifically expressed in the brain (Sutcliffe et al., 1984). This cross-hybridization was due to the presence of an 82 base ID element within the cDNA clones (Sutcliffe et al., 1982), a member of the SINE B2 family of retrotransposons homologous to tRNAs (Kramerov and Vassetzky, 2011). Although ID elements were initially presumed to be enriched in brain-specific transcripts (Sutcliffe et al., 1982), current genome sequence information and gene annotation do not support this initial assumption. Instead, ID elements are widely distributed throughout the genome, with their numbers ranging from 200 to 120,000 copies in a given rodent genome (Kim et al., 1994). Despite these ID elements typically being
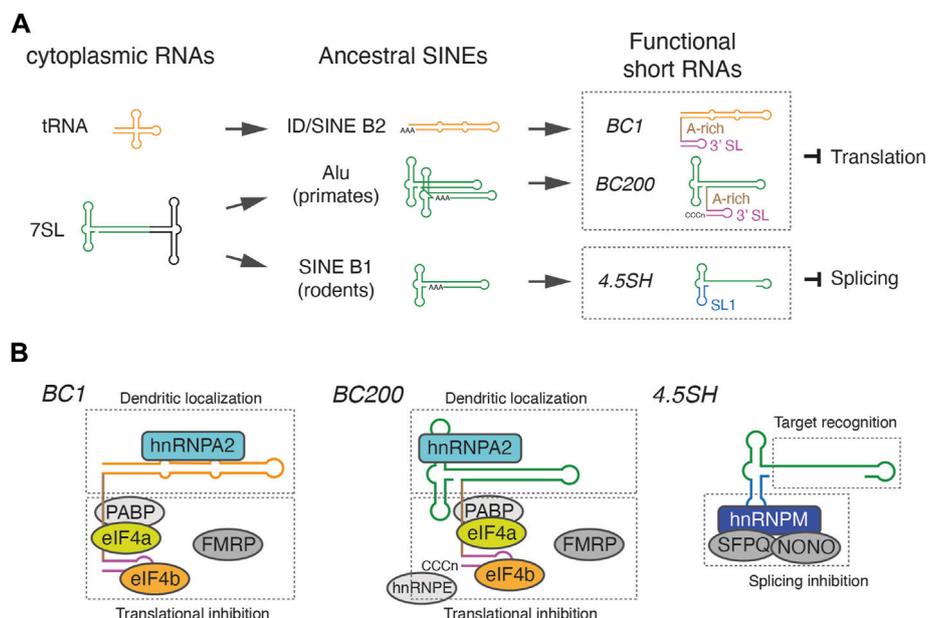

FIGURE 1
Origin of retrotransposon-derived short ncRNAs and their modular structures. **(A)** Schematic representation of the evolutionary origin of BC1, BC200, and 4.5SH RNA. BC1 and BC200 are derived from distinct SINEs, ID and Alu respectively, but independently acquired an A-rich linker and 3′ stem-loop (SL) structure to become functionally similar translational inhibitors. 4.5SH RNA acquired a unique stem-loop 1 (SL1) that associates with splicing repressors. **(B)** The modular organization of functional short RNAs. BC1 and BC2 associate with a similar set of proteins that mediate dendritic localization or translational inhibition. 4.5SH RNA consists of an effector binding module and a target recognition module, which bind splicing inhibitor proteins and base pair with target exons, respectively.

silenced and not transcribed into RNAs, *BC1*, which is highly homologous to *ID* elements, is abundantly expressed in the brain. *BC1* is a single copy gene in rats, while two copy loci have been identified in guinea pigs, possibly due to a DNA-mediated duplication event (Kim et al., 1994). *BC1* RNA is transcribed by RNA polymerase III and measures approximately 150 nucleotides in length (DeChiara and Brosius, 1987). *BC1* is thought to have originated from a *tRNA*[Ala (CGC)], however, evolutionary base substitution led to a significant reorganization of the secondary structure. Instead of forming the well-known clover-leaf structure typical of *tRNAs*, the 5′ region of *BC1* homologous to *tRNA* (or *ID*) forms a single long stem loop structure (Rozhdestvensky et al., 2001). The 5′ stem loop of *BC1* RNA is followed by an A-rich linker region and a 3′ stem loop sequence, both unique to *BC1* (Rozhdestvensky et al., 2001) (Figure 1A).

BC1 exhibits a unique distribution pattern, being specifically enriched in the dendrites of various types of neurons (Tiedge et al., 1991), a localization mediated by its 5′ stem loop structure through association with hnRNPA2 (Muslimov et al., 2006; Muslimov et al., 2011). This has led to long-standing speculation that *BC1* could control local translation at synaptic terminals. The first concrete evidence that *BC1* can inhibit translation came from *in vitro* studies. *BC1* has been shown to inhibit the *in vitro* translation of mRNAs in reticulocyte lysates in a manner dependent on eIF4A, an ATP-dependent helicase required for translational initiation (Wang et al., 2002). It is postulated that *BC1* may repress translation through multiple pathways (Figure 1B). The central A-rich linker of *BC1* directly binds to eIF4A, inhibiting its helicase activity (Lin et al., 2008; Eom et al., 2011). This A-rich linker also binds to PABP, which may also contribute to the translation inhibition by *BC1* (Wang et al., 2002). The 3′ stem loop of *BC1* associates with eIF4B, inhibiting its interaction with the small ribosomal subunit (Eom et al., 2011). Upon neuronal stimulation, eIF4B is dephosphorylated and dissociates from *BC1*, suggesting that *BC1*-mediated translational inhibition is controlled by neuronal activities (Eom et al., 2014).

The physiological significance of *BC1* has been illuminated through a series of studies utilizing *BC1* knockout (KO) mice. While *BC1* KO mice do not exhibit gross morphological abnormalities (Skryabin et al., 2003), behavioral studies have identified a decrease in exploratory behavior and an increase in anxiety in these mice (Lewejohann et al., 2004). At the electrophysiological level, dopamine-mediated synaptic regulation responses in striatal neurons and GABA-mediated spontaneous inhibitory activities are both enhanced in *BC1* KO mice (Centonze et al., 2007; Centonze et al., 2008). Notably, *BC1* KO mice demonstrate a pronounced increase in susceptibility to high-decibel (dB) auditory stimuli, with exposure to 120-dB sound potentially causing seizures or even death (Zhong et al., 2009). In these mice, mGluR-stimulated translation is anomalously upregulated, leading to the overexpression of synaptic proteins, including FMRP and PSD-95, upon mGluR activation. Electrophysiological studies reveal heightened synaptic activities in *BC1* KO mice, potentially explaining their extreme sensitivity to sound stimuli. This phenotype can be mitigated by the administration of anisomycin, a translational inhibitor, further supporting the notion that *BC1* typically attenuates local protein translation induced by neural stimuli (Zhong et al., 2009). More

recent studies suggest that *BC1* RNA regulates the structural plasticity of pyramidal neurons by inhibiting the translation of synaptic proteins, which results in enlarged synaptic spines in *BC1* KO mice (Briz et al., 2017).

In terms of the molecular mechanisms that inhibit translation at synaptic terminals, it was previously proposed that *BC1* binds to FMRP, an RNA-binding protein abundant in dendrites (Richter and Zhao, 2021), and recruits this translational inhibitor to target mRNAs with sequences complementary to *BC1* (Zalfa et al., 2003). Indeed, *BC1* and FMRP partially colocalize at striatal axon bundles, and GABA transmission is similarly upregulated in both FMRP/*BC1* double knockout (dKO) mice and single knockout of either gene (Centonze et al., 2008). However, later studies revealed that FMRP binds various types of mRNAs and other RNAs in a sequence non-specific manner, including *BC1* and FMRP-regulated target mRNAs (Iacoangeli et al., 2008). Furthermore, double knockout (dKO) mice lacking both FMRP and *BC1* exhibit increased responses to loud sounds compared to single KO mice (Zhong et al., 2010). This genetic interaction suggests that FMRP and *BC1* may regulate translation independently, potentially via distinct mechanisms. Recent findings that FMRP forms liquid droplets could reconcile these contradicting interpretations (Tsang et al., 2019). The C-terminal region of FMRP, known to be highly disordered, facilitates multivalent weak interactions necessary for the formation of phase-separated liquid droplets that contain RNAs *in vitro* (Tsang et al., 2019). Typically, intrinsically disordered regions of certain proteins interact with various RNAs in a sequence-independent manner, leading to the formation of phase-separated granules (Protter et al., 2018). The formation of mRNA-containing granules through FMRP may establish a molecular environment conducive to efficient translational inhibition by multiple mechanisms, including *BC1*-mediated translational suppression. Consequently, while the interaction between FMRP and *BC1* may be non-specific, they appear to be functionally interconnected.

BC200: primate-specific short RNA function as a translational regulator in dendrites

The original identification of *BC200* RNA resulted from the cross-hybridization of *ID* probes (which are *tRNA*-derived *SINEs*) to monkey RNA (Watson and Sutcliffe, 1987). These *ID* probes had previously been used to identify *BC1* RNA (Sutcliffe et al., 1982). However, *BC200* RNA shares significant sequence homology with *Alu* (a *SINE* derived from *7SL* RNA), rather than with *tRNA*-derived *SINEs* such as *ID* (Watson and Sutcliffe, 1987) (Figure 1A). This seemingly contradictory outcome can be explained by the fortunate presence of short sequences complementary to *Alu* in the *ID* probe (Watson and Sutcliffe, 1987). Despite their differences in origin and primary sequences, *BC1* and *BC200* share numerous common properties: both are short RNAs transcribed by RNA polymerase III, exclusively expressed in the brain, and localized in the dendrites of specific neurons (Tiedge et al., 1991). Both are composed of three distinct domains: the 5′ element homologous to *Alu*, the central A-rich domain, and the unique C-rich 3′ stem-loop structure (Martignetti and Brosius, 1993). Similar to *BC1*, *BC200* localizes
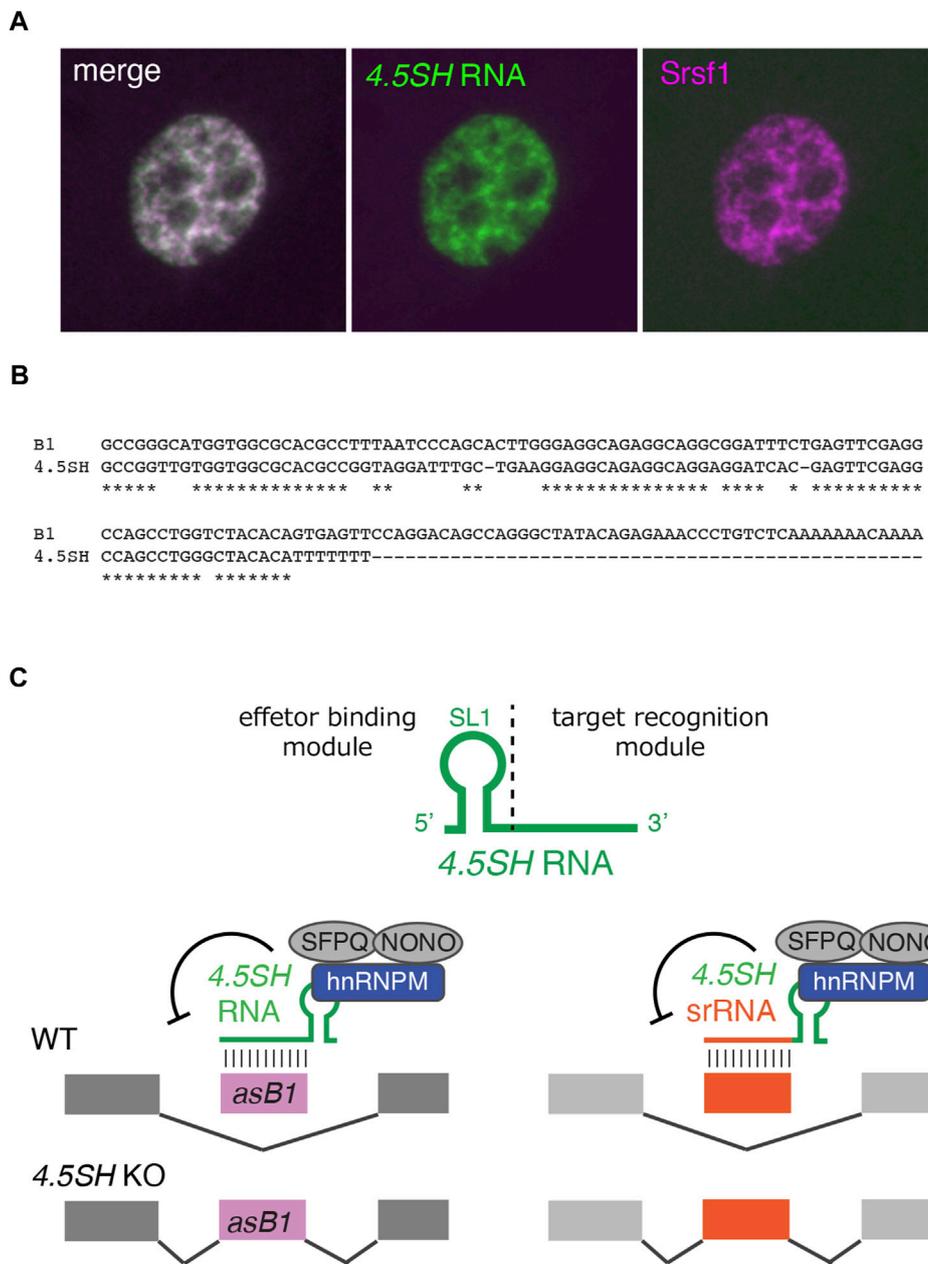
FIGURE 2
4.5SH induces skipping of deleterious exons. **(A)** Subcellular localization of *4.5SH* RNA in 3T3 cells. *4.5SH* RNA (green) is localized to nuclear speckles enriched in splicing regulators such as Srsf1 (magenta). **(B)** Alignment of *4.5SH* RNA and *SINE B1*. *4.5SH* RNA is highly homologous to *SINE B1* but lacks 3′ A-rich sequences required for retrotranspositions. **(C)** Schematics of *4.5SH*-mediated exon skipping and the generation of artificial splicing regulators. *4.5SH* RNA base pairs with antisense insertions of *SINE B1* (*asB1*) and inhibits their exonizations. In the *4.5SH* KO cells, these *asB1*-containing exons are abnormally included in hundreds of host transcripts, introducing premature stop codons and frame-shift mutations, leading to embryonic lethality. The modular organization of *4.5SH* RNA enables the generation of programmable splicing regulatory RNA (srRNA) consisting of the effector binding module of *4.5SH* RNA and sequences complementary to target exons of interest.

to dendrite through 5′ stem loop region that associates with hnRNPA2 (Muslimov et al., 2006; Muslimov et al., 2011; Muslimov et al., 2019), directly binds to eIF4a/eIF4b *in vitro* and inhibits translation (Lin et al., 2008; Eom et al., 2014), associates with PABP via the A-rich central domain (Muddashetty et al., 2002; Kondrashov et al., 2005), and forms a complex with FMRP (Zalfa et al., 2003) (Figure 1B). As a result, *BC200* RNA influence mRNA translation in a similar fashion to *BC1* RNA. Thus, these two

ncRNAs, despite originating from completely different groups of *SINE*s, may play a convergent role in negatively regulating local translation at the synapse.

In addition to these common protein components, *BC200* has been found to associate with a unique set of proteins. The 5′ region of *BC200* is highly homologous to *7SL*, an RNA component of signal recognition particles (SRP), and binds to SRP9/14 (Kremerskothen et al., 1998). *BC200* also binds to the Synaptotagmin Binding

Cytoplasmic RNA Interacting Protein (SYNCRIP) via the central A-rich linker domain (Duning et al., 2008), and to HNRNPE1 and HNRNPE2 via the 3′-located C-rich domain (Jang et al., 2017). Since *in vitro* translation inhibition mediated by *BC200* is counteracted by the addition of HNRNPE1/2, these proteins might function as cellular regulators to control local translation in dendrites (Jang et al., 2017).

Although no inherited diseases have been directly associated with *BC200*, it has been implicated in a variety of disorders such as cancers and neurodegenerative diseases. For instance, *BC200* is found in abnormally high levels in Alzheimer's disease (Mus et al., 2007) and in various cancers (Chen et al., 1997). *BC200* is also thought to be involved in the regulation of alternative splicing of apoptosis-related genes, such as Bcl-x, in breast cancer (Singh et al., 2016). Additional requirements for specific article types and further information please refer to "Article types" on every Frontiers journal page.

4.5SH RNA: a novel splicing regulator that function as a molecular antidote for toxic exonization of *SINE B1* in small rodents

4.5SH RNA, a 90-nucleotide nuclear ncRNA, was initially identified in the 1970s as an RNA that co-purified with poly-A (+) RNAs (Jelinek and Leinwand, 1978; Harada et al., 1979; Harada and Kato, 1980; Leinwand et al., 1982). This RNA is specifically found in a group of small, short-lived rodents, including mice, hamsters, and rats (Gogolevskaya et al., 2005). *4.5SH* RNA shares substantial homology with *SINE B1*, the most abundant *SINE* in rodent species, and is believed to have originated from the ancient B1 subfamily *pB1d10* (Quentin, 1994; Gogolevskaya et al., 2005) (Figures 1A, 2B). Unlike *BC1* or *BC200*, *4.5SH* is a multicopy gene. Contrary to ancestral *SINEs* that are interspersed throughout the genome, *4.5SH* forms a large cluster at a specific genomic region in each species. In the case of the mouse, the transcription unit of *4.5SH* is embedded in a 4.2 kb fragment, which is arranged in tandem to form large clusters of ~200 copies in a ~900 MB region of chromosome 6 (Schoeniger and Jelinek, 1986; Yoshimoto et al., 2022). Interestingly, while the *4.5SH* transcription unit is highly conserved, the other regions of the 4.2 kb repeat unit exhibit less conservation, suggesting the functional importance of *4.5SH*. The expression level of *4.5SH* RNA is exceptionally high, with over 10,000 molecules produced per cell (Schoeniger and Jelinek, 1986), and these transcripts are localized in nuclear speckles (Ishida et al., 2015) (Figure 2A), nuclear compartments containing poly-A (+) RNAs as well as splicing factors (Spector and Lamond, 2011). *4.5SH* RNA has been demonstrated to interact with multiple proteins, including La and Nucleolin (Leinwand et al., 1982; Hirose and Harada, 2008). Despite these molecular descriptions, the biological functions of *4.5SH* remained largely unknown for more than 40 years since its early discovery.

The first molecular function of *4.5SH* was demonstrated through experiments using antisense oligonucleotides (ASO) to deplete this nuclear ncRNA (Ishida et al., 2015). Treating murine cells, such as Neuro2A or 3T3, with ASO led to decreased cellular proliferation, whereas no such effect was observed in human cells that lack the *4.5SH* gene. Remarkably, *4.5SH* RNA formed an intra-molecular double-stranded RNA structure with reporter mRNAs that contain

antisense insertions of *SINE B1* (*asB1*) in the 3′ untranslated region, detectable by A to I base substitution dependent on the adenosine deaminase ADAR that recognizes a long stretch of double-stranded RNA (Ishida et al., 2015). However, the precise molecular mechanisms leading to decreased cellular proliferation remained unclear.

More definitive evidence for the molecular and physiological functions of *4.5SH* RNA comes from very recent studies using knockout (KO) mice (Yoshimoto et al., 2022). The mutant mice exhibited early embryonic lethality, suggesting that *4.5SH* is an essential gene in mice. Subsequent analyses of RNA-Sequencing data led to the discovery of hundreds of exons that were aberrantly included in *4.5SH* KO cells. Notably, 75% of these KO-enriched exons were unannotated in RefSeq and were identified as cryptic exons. A detailed examination of these abnormal exons revealed that their consensus sequences matched *asB1*. Indeed, *asB1* naturally contains near-consensus splicing acceptor and donor sequences, excluding the branch point sequences (Sela et al., 2007). Hence, when *asB1* is inserted downstream of branch point consensus sequences in introns, it can potentially introduce deleterious premature stop codons or induce frameshift mutations. *4.5SH* counteracts the toxic exonization of *asB1*, serving as a molecular antidote that protects the transcriptome from the aberrant inclusion of *asB1* (Figure 2C).

Mechanistically, *4.5SH* RNA consists of two modules: the 5′ effector-binding module and the 3′ target recognition module (Yoshimoto et al., 2022). The 5′ effector-binding module features a characteristic stem-loop structure and associates with splicing inhibitory effector proteins, including Hnrnpm, Sfpq, and Nono. The complexes are recruited to *asB1*-containing exons via the 3′ target recognition region, which base pairs with the complementary *asB1* sequences. Interestingly, the modular organization of *4.5SH* RNA offers an opportunity to engineer programmable splicing regulator RNAs (srRNAs) (Figure 2C). By replacing the target recognition module with sequences complementary to exons of interest, one can create a chimeric srRNA that induces skipping of target exons. This finding opens up new avenues in genetic research, with potential applications as a molecular biology tool and as a basis for RNA therapeutics.

Concluding remarks

The field of ncRNAs continues to reveal increasingly complex regulatory networks influencing cellular physiology and pathology (Mattick et al., 2023). This review focused on three retrotransposon-derived short RNAs–*BC1*, *BC200*, and *4.5SH* RNA–highlighting the multifaceted roles of ncRNAs. Intriguingly, the functions of these short ncRNAs appear to have been acquired independently throughout each species' evolution, not confined by their ancestral origin: *BC1* and *BC200*, derived from *tRNA* and *7SL*, respectively, seem to have undergone convergent evolution to become translation inhibitors. Conversely, *4.5SH*, derived from *7SL*, has obtained nuclear localization properties unlike *BC200*, evolving to become a splicing regulatory ncRNA, possibly through modification of the 5′ stem loop structure that binds strongly to Hnrnpm, a splicing inhibitor (Yoshimoto et al., 2022).

A pertinent question is why these short ncRNAs emerged in a species-specific manner despite their essential roles during development (as seen with *4.5SH* RNA) or under certain

environmental conditions (as with *BC1*). They may have co-evolved with the stochastic emergence of deleterious *SINE* insertions. For instance, the insertion of the exonization-prone *asB1* into the intron of an essential gene may give rise to toxic exons detrimental to animal survival. However, if this happens in animals expressing ancestral *4.5SH*, the intronic *asB1* insertions are likely neutral and don't substantially affect the transcriptome's integrity. Hence, *SINE B1* can freely propagate and embed its copy without harm in animals expressing *4.5SH* RNA, and the copy number of *4.5SH* also increases to suppress the rising number of potentially toxic exons. The same scenario might be applicable to the emergence and evolution of *BC1* and *BC200*, especially if the insertions of the complementary retrotransposon into the $3'$ UTR of certain neuronal genes could affect harmful effects by enhancing the translation of the host mRNAs.

It is crucial to emphasize that there are other *SINE*-derived or repeat-derived short ncRNAs whose functions have not been fully elucidated (Matylla-Kulinska et al., 2014; O'Neill, 2020). Future research on these ncRNAs will not only deepen our understanding of gene regulation complexities but also offer potential implications for the diagnosis, prevention, and treatment of human diseases. We anticipate that the insights presented here will spur further studies and potential applications for these fascinating RNAs.

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RY: Conceptualization, Funding acquisition, Writing–original draft, Writing–review and editing. SN: Conceptualization, Funding acquisition, Writing–original draft, Writing–review and editing.

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Conflict of interest

RY and SN declare that a patent application has been submitted based on the paper "Yoshimoto et al., 2022".

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