Molecular Therapy
Review

Roles of lncRNAs in brain development and pathogenesis: Emerging therapeutic opportunities

Tara Srinivas,[1] Carolina Mathias,[2,3] Cristina Oliveira-Mateos,[1] and Sonia Guil[1,4]

[1]Josep Carreras Leukaemia Research Institute (IJC), Badalona, 08916 Barcelona, Catalonia, Spain; [2]Department of Genetics, Federal University of Parana, Post-graduation Program in Genetics, Curitiba, PR, Brazil; [3]Laboratory of Applied Science and Technology in Health, Carlos Chagas Institute, Oswaldo Cruz Foundation (Fiocruz), Curitiba, PR, Brazil; [4]Germans Trias i Pujol Health Science Research Institute, Badalona, 08916 Barcelona, Catalonia, Spain

The human genome is pervasively transcribed, producing a majority of short and long noncoding RNAs (lncRNAs) that can influence cellular programs through a variety of transcriptional and post-transcriptional regulatory mechanisms. The brain houses the richest repertoire of long noncoding transcripts, which function at every stage during central nervous system development and homeostasis. An example of functionally relevant lncRNAs is species involved in spatiotemporal organization of gene expression in different brain regions, which play roles at the nuclear level and in transport, translation, and decay of other transcripts in specific neuronal sites. Research in the field has enabled identification of the contributions of specific lncRNAs to certain brain diseases, including Alzheimer's disease, Parkinson's disease, cancer, and neurodevelopmental disorders, resulting in notions of potential therapeutic strategies that target these RNAs to recover the normal phenotype. Here, we summarize the latest mechanistic findings associated with lncRNAs in the brain, focusing on their dysregulation in neurodevelopmental or neurodegenerative disorders, their use as biomarkers for central nervous system (CNS) diseases *in vitro* and *in vivo*, and their potential utility for therapeutic strategies.

INTRODUCTION

Over the last decade, long noncoding RNAs (lncRNAs; with an arbitrary cutoff size of >200 nt) have been the object of intense study, and research addressing their mechanisms of action as well as their contribution to human pathophysiology has multiplied. We now understand the important roles that lncRNAs play in normal cellular function, including growth and death, development and differentiation, and metabolic homeostasis. Characterization of these functions has allowed a greater understanding of the molecular underpinnings of lncRNA action. In the nucleus, lncRNAs can associate with chromatin remodeling complexes, act as co-transcriptional factors, and regulate stages of RNA biogenesis, maturation and localization. In the cytoplasm, they can influence the fate of other RNA or protein molecules by acting as signaling molecules, molecular decoys, scaffolds, cofactors, and targeting agents.

Recent reviews highlight the detailed actions of the best-characterized lncRNAs.[1] Briefly, lncRNAs regulate gene expression through multiple mechanisms. In the nucleus, lncRNAs may collaborate in 3D chromatin organization and/or remodeling, chromatin modification, transcription and splicing control, or even mRNA export. In the cytoplasm, they may influence the stability, localization or translation of other RNAs; function as molecular sponges of other RNAs or proteins; or regulate post-translational modifications. This myriad of functions is achieved through the general ability of lncRNAs to interact, through different structured domains, with multiple nucleic acids and proteins, often simultaneously. Most of these functions have been studied in the context of tumorigenesis, but prominent roles have been found in other pathological contexts too, including cardiovascular diseases,[2] inflammatory disorders,[3] and diabetes.[4]

In the nervous system, neuronal maturation, plasticity, and homeostasis are well-orchestrated, complex mechanisms that rely largely on timely regulation of RNA production, localization, and decay. lncRNAs are involved at all stages in these processes; it is therefore unsurprising that the central nervous system (CNS) displays the richest landscape of noncoding RNA species and lncRNA-based regulatory mechanisms, with approximately 40% of all annotated tissue-specific lncRNAs existing in distinct brain regions.[5,6] We review the most relevant roles of lncRNAs in the brain with an emphasis on the latest advances, presenting evidence for the value of lncRNAs as biomarkers and perspectives for lncRNAs as *bona fide* therapeutic targets or tools in the treatment of CNS disorders.

lncRNAs IN THE BRAIN: EVOLUTION AND FUNCTION

lncRNAs are generally poorly conserved, and despite the fact that approximately one-third of them appear only in the primate lineage,[7,8] brain-specific lncRNAs show the highest evolutionary conservation.[9] One caveat of these estimations is the fact that structural features, rather than the primary nucleotide sequence, are often the

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Correspondence: Sonia Guil, Josep Carreras Leukaemia Research Institute (IJC), Badalona, 08916 Barcelona, Catalonia, Spain.
E-mail: sguil@carrerasresearch.org

determinants of functionality for lncRNAs. This phenomenon is well illustrated by *Xist*, a crucial lncRNA for X chromosome inactivation,[10,11] and the metastasis associated lung adenocarcinoma transcript 1 *MALAT1*, a very abundant transcript with highly conserved helices in its functional core.[12,13] Importantly, the abundance of lncRNAs produced by an organism correlates with tissue- or organism-specific complexity,[11,14] which argues for a contribution of the brain-specific lncRNAs to CNS development. In this regard, prominent examples of relevant lncRNAs in the brain include *linc-Brn1b* and *Dali* (which bind epigenetic modifiers and regulate genes required for neocortical development[15,16]), or *Pnky* (which is highly expressed in neural stem cells of the developing cortex and interacts with splicing regulators[17]). These noncoding transcripts represent a common theme in brain-specific lncRNAs: conserved intergenic lncRNAs located adjacent to and co-expressed with protein-coding genes are often involved in large-scale transcriptional programs in CNS development.[18] Sometimes, short-range action by lncRNAs is compatible with the regulation of distal sites in *trans*, often involving binding to chromatin remodeling complexes and reorganization of the 3D genome. For example, *Paupar* is a CNS-specific lncRNA that acts locally to regulate the expression of the nearby neural transcription factor *Pax6* as well as distally by interacting with regulatory elements of multiple genes on different chromosomes.[19–21] Interestingly, the action of *Paupar* in *trans* also involves binding to the PAX6 protein itself to regulate target gene transcription at multiple distal genomic sites, which illustrates how lncRNAs and neural transcription factors can interact to orchestrate cortical differentiation.[22] Other examples of nuclear enriched lncRNAs that operate similarly include *Evf2* (which interacts with transcription factors and chromatin remodelers to regulate expression of neuronal genes and drive lineage specification)[23–25] and *Gm12371* (which targets multiple genes through regulation of other lncRNAs and is necessary for synaptic transmission in hippocampal neurons).[26]

Structural lncRNAs in the brain

Some structural lncRNAs with critical roles in brain function deserve special mention: nuclear paraspeckle assembly transcript 1 (*NEAT1*) and metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*) are two highly conserved and expressed nucleus-retained lncRNAs with structural and regulatory roles.[27–30] Although ubiquitously present in different tissues, they are some of the most abundant lncRNAs in the brain cortex[31] and are involved in normal neuronal function as well as in the pathophysiology of neurological disorders.[32,33] Indeed, *MALAT1* and *NEAT1* constitute the major RNA moiety and scaffold of two important subnuclear domains, speckles and paraspeckles, respectively, which regulate the localization and phosphorylation status of splicing factors and other RNA binding proteins, mRNAs, and transcription factors.[34] Although prominent roles of *MALAT1* in neuropathology are well established,[35] *MALAT1* function and the impact of its dysregulation have been studied mostly in the context of cancer. By contrast, the impact of *NEAT1* function in the CNS deserves special mention when considering the molecular underpinnings of neuropathology. *NEAT1* may contribute to phase separation of intrinsically disordered regions, forming a non-membranous ribonucleoprotein milieu that provides a flexible platform for assembly of a number of protein and nucleic acids components. For example, binding to *NEAT1* facilitates the condensation propensity of transactive response DNA binding protein of 43 kDa (TDP-43), a DNA and RNA binding protein (RBP) involved in splicing regulation that forms protective nuclear bodies in response to stress, defects in which (e.g., aberrant phosphorylation, cytoplasmic mislocalization, and aggregation) contribute to amyotrophic lateral sclerosis (ALS).[36] Alterations in TDP-43 are also typical of other neurological diseases, such as Alzheimer's disease or frontotemporal lobar degeneration (FTLD).[37] Individual-nucleotide resolution cross-linking immunoprecipitation data reveal multiple TDP-43 binding regions at the 5′ and 3′ ends of *NEAT1* transcripts, with specific enrichment at UG repeat regions.[37,38] This binding preference is consistent with the particular structure of *NEAT1* transcripts, where core and structural members of paraspeckles (such as the architectural proteins PSPC1, p54nrb/NONO, and SFPQ) bind along the central region of the transcript,[39] whereas auxiliary proteins (e.g., TDP-43) are more present at the periphery (i.e., the paraspeckle shell).[40]

Despite the existence of a relatively large body of literature about *NEAT1* and TDP proteinopathies, the specific mechanism whereby *NEAT1* modulates the capacity of TDP-43 and other RBPs for ribonucleoprotein assembly and regulation of transcriptional and post-transcriptional events under physiological conditions remains elusive,[41] as does the specific contribution of *NEAT1* to TDP-43 mislocalization and the subsequent impact of this mislocalization on mRNA splicing in neurodegeneration.[42] Thus, further studies addressing the detailed biophysical properties and roles of *NEAT1* and paraspeckles as a hub of RBP function and/or in phase separation are needed for a full understanding of the potential protective role of *NEAT1* in these types of proteinopathies (Figure 1).

In addition, interesting insights into the neurobiology of *NEAT1* and paraspeckles arise from the observation that the RNA and protein components of paraspeckles follow circadian rhythms, resulting in nuclear retention of specific transcripts in a paraspeckle-dependent manner that follows rhythmic circadian retention and expression patterns.[43] Further research indicates that *NEAT1* directly binds to 30% of all transcripts targeted by paraspeckles, suggesting that protein:RNA and RNA:RNA interactions are involved in nuclear retention of mRNAs by paraspeckles.[44] Although the detailed mechanisms involved in circadian nuclear retention of mRNAs remains to be determined, this evidence suggests that paraspeckles may play important roles in controlling circadian gene expression at a post-transcriptional level, thereby contributing to the adaptation of organisms to regular changes in their environment. It remains to be investigated whether dysregulation of this circadian control plays roles in human diseases such as neuropsychiatric disorders. Another recently uncovered *NEAT1* function with potential impact in brain disorders is its connection with mitochondrial function. The use of genome-wide RNAi screens has revealed genes involved in mitochondrial homeostasis to regulate *NEAT1* and paraspeckle formation, suggesting an unexpected link between mitochondria and nuclear bodies.

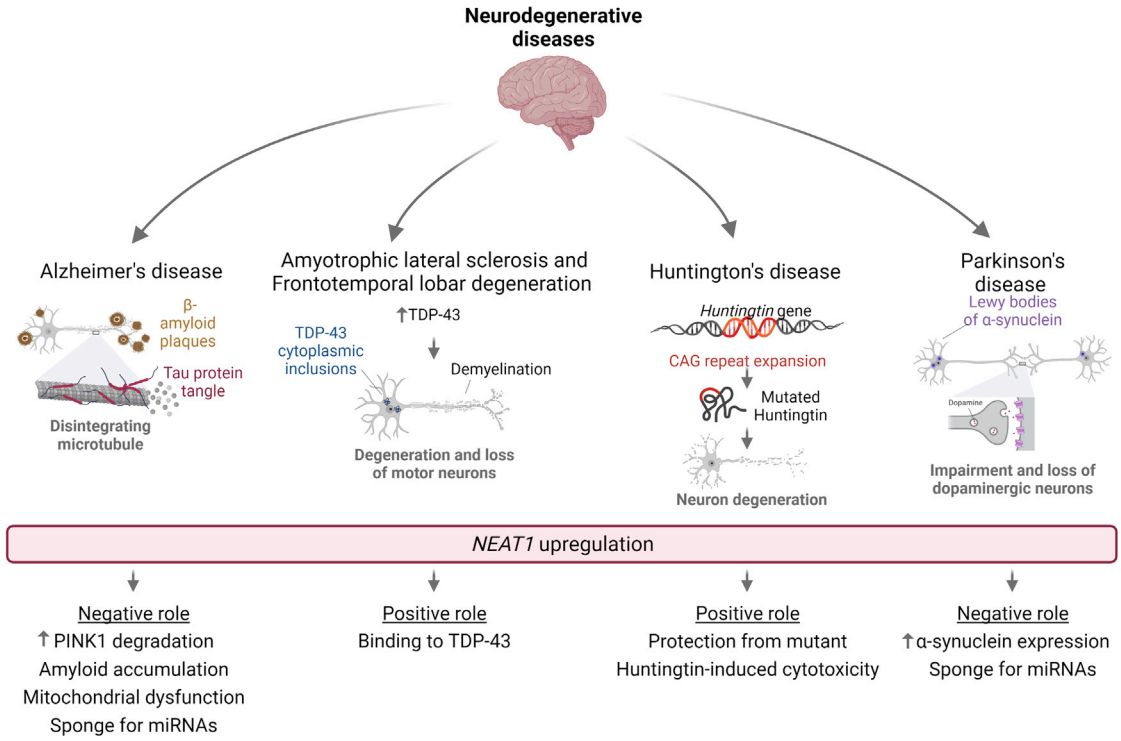

Figure 1. Impact of *NEAT1* and paraspeckles on NDs

Alzheimer's disease (AD) is frequently characterized by accumulation of β-amyloid peptide and disruption of microtubules because of Tau protein tangles. Amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD) share molecular features, such as an increase of TDP-43 leading to cytoplasmic inclusions and demyelination with consequent loss of motor neurons. Huntington's disease (HD) is caused by a CAG tri-nucleotide repeat expansion in the Huntingtin (HTT) gene that promotes neuron degeneration. PD disease is characterized by formation of Lewy bodies, a consequence of aggregation of α-synuclein protein, and dysfunction of dopaminergic neurons. The common alteration in all of these diseases is upregulation of *NEAT1* with diverse effects. In AD, it has a negative influence, acting as a sponge for miRNAs and promoting amyloid accumulation and mitochondrial dysfunction by *PINK1* degradation. In ALS and FTLD, *NEAT1* plays a neuroprotective role by binding to TDP-43 and facilitating its phase separation to prevent accumulation of prion-like aggregates. In HD, it prevents cytotoxicity induced by mutant HTT, and in PD, it increases α-synuclein expression and acts as a sponge for miRNAs. This figure was created with BioRender.

Indeed, mitochondrial stressors alter *NEAT1* expression by activating transcription factor 2 (ATF2)-mediated transcriptional upregulation, consequently disrupting paraspeckle morphogenesis. Specifically, mitochondrial stress and altered *NEAT1* expression increase the nuclear retention of mRNAs encoding for mitochondrial proteins (so-called mito-mRNAs). Accordingly, treatments that directly alter *NEAT1* levels also have an impact on mitochondrial function by changing the retention of some of these mito-mRNAs and causing aberrant mitochondrial homeostasis, pointing to a dynamic cross-talk between mitochondria and paraspeckles in response to changing cellular conditions.[45] More generally, the emerging picture is that *NEAT1* and paraspeckles act as sensors of a variety of stress signals and mediate important changes in gene expression to allow cellular adaptation to new conditions[46] (Figure 2).

CONTRIBUTION OF lncRNAs TO NORMAL BRAIN CELL PHYSIOLOGY

lncRNAs may have important roles in physiological neuronal growth and plasticity, thus impacting cognitive functions. For example, depletion of *NEAT1* with small interfering RNAs (siRNAs) or following neuronal potassium chloride stimulation reduces the levels of lysine 9 di-methylation on histone H3 (H3K9me2) at the *c-Fos* promoter (likely by impairing *NEAT1* regulation of the histone methyltransferases EHMT1/2) and consequently upregulates the transcription complex activator protein-1 (AP-1), whose activity is linked to hippocampus-dependent learning tasks.[47] In accordance with this link between *NEAT1* and neuronal activity, a recent study has provided new insights to understand the impact of knocking out *Neat1* in the mouse CNS. Depletion of murine *Neat1* expression has a robust phenotype characterized by compromised secretory function and development of critical tissues relating to female reproduction.[48,49] While *Neat1* knockout mice do not present with an overt neurological phenotype, some deficits may only manifest under certain stress conditions. Indeed, *Neat1* knockout (KO) animals suffer under specific stress conditions because of altered neuronal excitability and changes in the alternative splicing patterns of certain genes important for CNS function. These $Neat1^{-/-}$ mice present a distinct behavioral phenotype following a stressful stimulus, which includes hyperlocomotion, decreased anxiety, and impaired sociability, without any apparent neuroinflammation or gross synaptic dysfunction. *NEAT1* likely

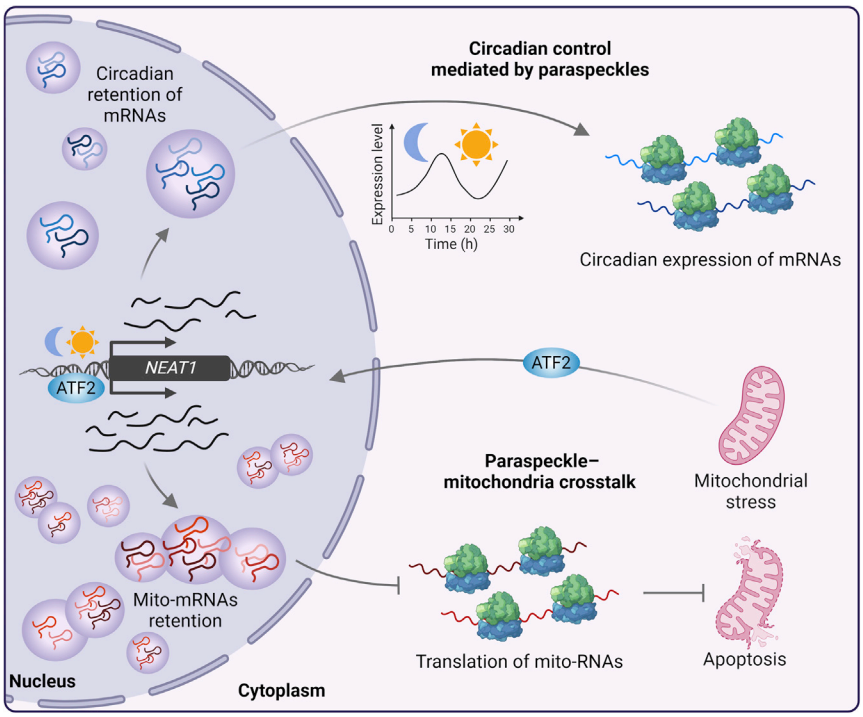

Figure 2. Alternative roles of *NEAT1* and paraspeckles: Impact on circadian gene expression and mitochondrial cross-talk

NEAT1, among other components of the paraspeckle, follows a circadian expression pattern. This leads to rhythmic retention of certain mRNAs in the paraspeckle, including some core-clock mRNAs, allowing control of their circadian expression. On the other hand, *NEAT1* regulates mitochondrial homeostasis and protects cells from apoptosis through the paraspeckle-mediated function. Mitochondrial stress favors *NEAT1* expression by activation of the transcription factor ATF2, which binds to its promoter. *NEAT1* upregulation correlates with an increase in the number of paraspeckles and adoption of an elongated morphology, together with enhanced retention of mRNAs. Among them, mRNAs of nucleus-encoded mitochondrial proteins (mito-mRNAs) conform an enriched group, and repression of their translation avoids induction of the mitochondrial pathway of apoptosis. This figure was created with BioRender.

fine-tunes neuronal excitability because *Neat1*$^{-/-}$ neurons are intrinsically hyperexcitable in culture and have deficiencies in calcium homeostasis. Molecularly, this is concomitant with altered expression of a subset of genes (including the riboflavin kinase [*Rfk*] gene, which is linked to regulation of circadian rhythms) as well as changes in the splice site choice of a subset of genes, some of which are genetically linked to psychiatric disorders such as schizophrenia and autism spectrum disorder.[50]

Cytoplasmically/synaptically enriched lncRNAs

The elaborate morphology of neurons confers special features to the subcellular localization of lncRNAs. The intriguing role of *NEAT1* in mediating nuclear retention of TDP-43 and its potentially protective roles in certain proteinopathies (Figure 3A) is described above. Additionally, cytoplasmic lncRNAs deserve special mention when considering neuronal function. Different lncRNA entities are finely regulated in their spatiotemporal patterns of expression in the different cytoplasmic subcompartments, suggesting important roles in synaptic plasticity, learning, and memory. As an example, the activity-dependent transported lncRNA (*Adeptr*) is localized to dendrites by the motor protein Kif2A in a cyclic AMP (cAMP)/protein kinase A (PKA)-dependent manner, where it has a role in maintaining proper localization of the actin-scaffolding regulators ankyrin and spectrin, thus contributing to structural plasticity at the synapse[51] (Figure 3B). The brain cytoplasmic 1 (*BC1*) lncRNA is also specifically transported to dendrites in association with other RBPs, such as Staufen, Translin, and the fragile X syndrome protein (FMRP).[52–55] *BC1* was the first ncRNA identified to have a role in mediating *de novo* protein synthesis at the synapse,[56] and its primate functional analog is *BC200*. *BC1*/*BC200* regulate the initiation phase of translation by directly interacting with eIF4A and eIF4B in dendritic spines, thereby inhibiting formation of the 48S pre-initiation complex.[57] However, different ribonucleoprotein complexes with the participation of *BC1*/*BC200* may affect translation differently. For example, in mouse models of Alzheimer's disease, the *BC1*-FMRP association has been reported to induce amyloid precursor protein (*APP*) mRNA translation, and inhibition of *BC1* protects against learning and memory deficits[58] (Figure 3C). It is unknown to what extent *BC200* lncRNA reproduces the functions of the mouse *BC1* in human physiopathology, specifically in neurodegenerative disease, and thus its involvement in disease etiology is unclear. Other cytoplasmic lncRNAs are also able to influence translation; the *BACE1-AS* lncRNA, which is transcribed in the antisense direction relative to the β-secretase 1 (*BACE1*) coding gene, is stabilized by the neuronal RNA-binding protein HuD and enhances *BACE1* mRNA levels and translation through partial base-pairing, with implications for the etiology of neurodegenerative disorders (see below).[59]

lncRNAs in the cytoplasm may also impact post-translational modifications and affect synaptic transmission. In the mouse hippocampus, the *Carip* lncRNA binds directly to the β subunit of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) and regulates post-translational modifications of target proteins (e.g., the excitatory α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptor subunits) in the postsynapse.[60,61] Indeed, *Carip* KO mice display significantly reduced levels of phosphorylated AMPA receptor (AMPAR) and NMDA receptor (NMDAR) subunits, decreased amplitude of postsynaptic excitatory currents, and attenuated long-term potentiation of the hippocampal CA3-CA1 synapses, causing learning and memory deficits in mice.

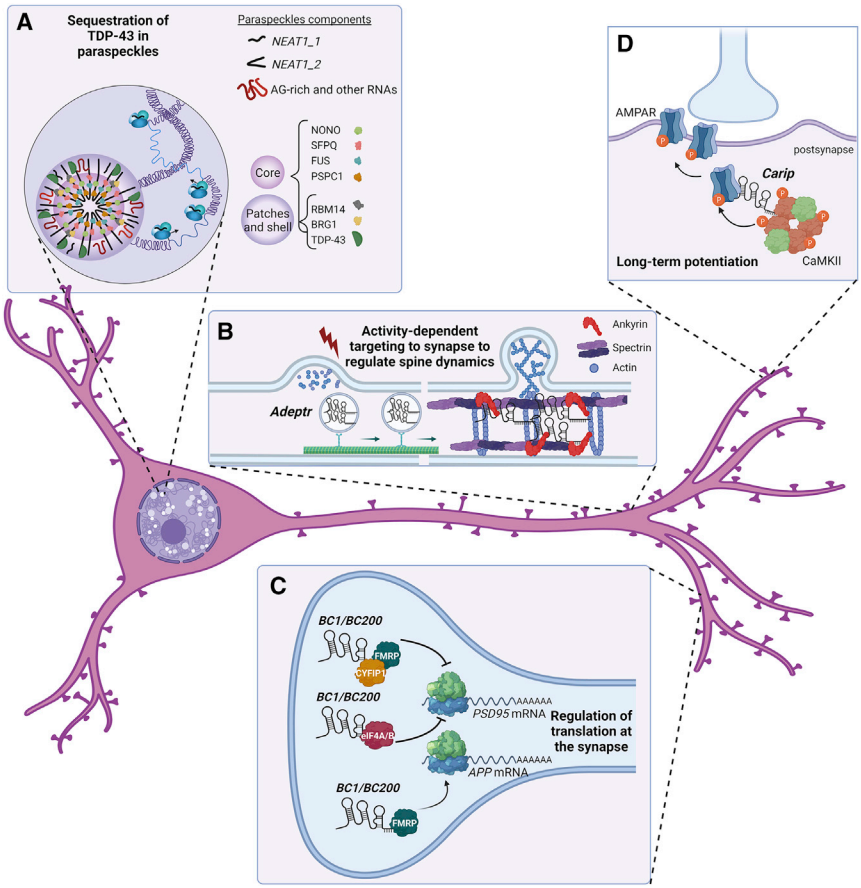

Figure 3. Examples of localized action of lncRNAs in neurons

(A) *NEAT1* upregulation may be protective in TDP-43 proteinopathies by mediating nuclear sequestration of TDP-43 in paraspeckles. (B) The lncRNA *Adeptr* is targeted to dendrites by the motor protein Kif2A upon neuronal activity, where it mediates a cAMP signaling-induced increase in spine density, supporting synaptic activity. Mechanistically, *Adeptr* acts as a scaffolding agent of at least two regulators of actin polymerization in neuronal dendrites: AnkyrinB and Spectrin. (C) In the wild-type (WT) mouse neocortex, binding of *BC1* lncRNA to the FMRP-CYFIP1 complex and to eIF4A/B at the synapse leads to repression of PSD-95 translation, preventing its exaggerated local synthesis. By contrast, in Alzheimer's mouse models, *BC1/BC200*-FMRP positively regulates *APP* mRNA translation. (D) In the hippocampus, binding of the β subunit of the CaMKII complex to the lncRNA *Carip* enhances phosphorylation of the AMPA receptor and increases conductance of the post-synaptic AMPAR channel, contributing to long-term potentiation and enhancing learning and memory.

Through dual binding, *Carip* is suggested to bridge and possibly stabilize the association between the active CaMKII complex and its substrates, the GluA1 and GluA2 subunits of the AMPAR; the mechanistic connection between *Carip* and NMDAR is less clear (Figure 3D). Although *Carip* is a conserved transcript also present in humans, it is unknown whether the human ortholog plays a similar role. Modulation of CaMKII might be a shared mechanism among multiple lncRNAs to regulate synaptic plasticity and cognitive processes. For example, upon ischemia, upregulation of the CaMKIIδ and γ subunits facilitates neuronal survival through promotion of IKKα/β signaling and activation of the nuclear factor κB (NF-κB) pathway. This signaling is in part controlled by the intragenic lncRNAs *C2dat1* and *C2dat2*, which overlap with the CAMK2D gene locus in the mouse genome. Downregulation of *C2dat1/2* cooperatively reduces CAMK2δ expression through a still unknown mechanism, exacerbating ischemia-induced neuronal death.[62,63]

Despite remarkable progress in the understanding of lncRNA functions in the brain, there are still large areas to be investigated. For example, few studies consider the stoichiometry of RNA-protein interactions, which are often imbalanced with generally low levels of lncRNA expression. In this regard, the contribution of subcellular condensates to the role of lncRNAs as scaffolds, competitors, or regulators of other molecules is intriguing. Future research can further characterize the diversity of mechanisms used by lncRNAs to modulate neuronal function as well as the contribution of noncoding transcripts to glial cells under physiological and disease conditions.[64] Additionally, little is known to date about the impact of lncRNA modifications (especially the most abundant N6-methyladenosine (m^6A) mark, a form of methylated adenosine) on their brain functions, although exciting recent advances foresee key roles of modified lncRNAs in neuronal development.[65]

lncRNAs AS BIOMARKERS IN DISORDERS OF THE CNS: DIAGNOSTIC RELEVANCE

Given the diverse functions of annotated lncRNAs in the CNS, the question of diagnostic and therapeutic utility arises. Here we summarize evidence regarding the use of lncRNAs in CNS disease association and treatment.

Neurodegenerative diseases

Neurodegenerative diseases (NDs) are characterized by progressive loss of nerve cell function and, at the molecular level, accumulation of misfolded proteins and oxidative stress.[66] They broadly include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), dementia, spinocerebellar ataxia (SCA), and ALS. ND patients present with loss of cognitive and/or motor function; however, given that the causes of many NDs remain unknown, there are currently no effective treatments.[67]

Emerging research reveals that lncRNAs may be more heavily involved in ND pathogenesis than previously assumed. For example,

BACE1-AS has been shown to stabilize *BACE1* mRNA *in vitro* in human cells and *in vivo* in murine brains.[68] BACE1-mediated proteolysis of APP leads to formation of hydrophobic β-amyloid peptide aggregates and senile deposits (hallmarks of AD pathophysiology).[69,70] These aggregates can increase transcription of *BACE1-AS*, driving an injurious feedforward APP processing cascade. Furthermore, expression of several lncRNA genes, including *BACE1-AS*, *51A*, and *LRP1-AS*, is upregulated in AD patient brains.[71–73] The utility of these studies in developing diagnostic criteria should be considered cautiously because it remains unclear whether and how elevated lncRNA expression mechanistically contributes to the causes rather than simply markers of AD. Additionally, data from large *in vivo* cohorts controlling for disease severity and, in the case of human samples, comorbidities are underrepresented in these studies.

Many other lncRNAs are similarly associated with PD, HD, and ALS and are being investigated *in vitro* and *in vivo*.[74] For example, recent findings highlight increased *NEAT1L* (the long isoform of *NEAT1*) expression in mouse models of polyglutamine diseases like HD, while loss of *NEAT1L* expression in dopaminergic neuroblastoma cell lines derived from HD patients leads to cellular dysfunction.[75] Identifying lncRNAs with a potential role in ND by minimally invasive sampling of patient populations could bolster mechanistic studies and supplement ND diagnosis before onset of severe clinical symptoms, although the sampling rationale and methods would need to be considered carefully in the context of disease. For example, while HD is a monogenic disorder, PD is a heterogeneous disease whose diagnosis could be aided by molecular pathological findings. Given that PD symptoms are marked by selective loss of nigrostriatal dopaminergic neurons,[76] it would be important to sample lncRNAs associated with PD (e.g., *NEAT1*, *TUG1*, and *UCA1*, which have not been studied consistently in dopaminergic neurons)[74] in this neuronal subpopulation to assess their specificity to the disease pathophysiology. The clinical practicality of neuronal subtype sampling is also an important consideration.

Cancer

Malignant brain tumors include primary and metastatic lesions characterized by uncontrolled cell growth, necrosis, and dynamic angiogenesis that often result in headache, seizures, loss of neurological function, and, ultimately, death.[77] While current noninvasive techniques (computed tomography [CT], magnetic resonance imaging [MRI], or positron emission tomography [PET] scans) are useful for identification, structural characterization, and broad localization of these tumors, it is difficult to classify tumor pathology and malignancy by noninvasive procedures alone. Definitive diagnosis by surgical biopsy is complicated by risks of intra- and post-operative functional decline.[78] Thus, optimizing noninvasive detection of brain tumor biomarkers in patients of all ages is a key unmet need in neuro-oncology.

lncRNAs have recently emerged as regulators of brain tumor progression and cell stemness.[79–81] Indeed, lncRNAs such as forkhead box D2 adjacent opposite strand RNA 1 (*FOXD2-AS1*), homeobox A (HOXA) distal transcript antisense RNA (*HOTTIP*), and HOX antisense intergenic RNA (*HOTAIR*) have been shown to promote glioma progression via cell cycle regulation and epigenetic alterations.[19,82–84] Importantly, certain lncRNAs that cross the blood-brain barrier (BBB) and become enriched in cerebrospinal fluid (CSF) are upregulated in gliomas *ex vivo*, making them potential biomarkers for brain cancer.[85] Although finding a universal marker for brain tumor patients is currently challenging, the ability to assay biomarker lncRNA expression from circulating tumor cells, exosomal noncoding RNAs, and CSF of cancer patients could greatly enhance the efficacy of brain tumor diagnosis. It remains to be seen, however, whether lncRNAs provide added value for brain cancer diagnosis/prognosis or therapy relative to other circulating species such as miRNAs, whose translational potential in cancer is advancing more rapidly.[86]

Neurodevelopmental disorders

Neurodevelopmental disorders (NDDs) encompass an array of clinical conditions including but not limited to autism spectrum disorder (ASD), fragile X syndrome (FXS), Down syndrome (DS), and Rett syndrome (RTT). They are broadly characterized by behavioral anomalies, intellectual disability, and motor symptoms. Because of their often complex and heterogeneous genetic etiology, NDDs can be difficult to diagnose and target therapeutically, and ongoing research is aimed at uncovering the molecular, genetic, and epigenetic landscape of these disorders.

Many lncRNAs are differentially expressed, mutated (including an increased burden of rare copy number variants of lncRNA loci in ASD), and/or pathogenically implicated in NDDs.[87–90] The lncRNAs *AK081227* and *AK087060* are significantly upregulated in RTT mouse brains and are associated with downregulation of the gene encoding the gamma-aminobutyric acid receptor Rho 2, a component of inhibitory neurotransmission.[91,92] Another class of noncoding RNAs, circular RNAs (circRNAs), shows links to NDD with emerging evidence of protein-regulatory roles in the brain.[93] circRNAs are noncoding RNA molecules that undergo intra-transcript back-splicing and covalent linkage to form continuous closed loops lacking 5′ to 3′ polarity.[94] Recently, dysregulation of noncoding ultraconserved and circRNAs has been shown to impact the biogenesis of AMPA receptors in RTT models.[95] Additionally, brain-derived neurotrophic factor (BDNF), which plays a role in neuronal maturation, survival, and growth,[96] is aberrantly diminished in RTT patients, and its antisense transcript, *BDNF-AS* lncRNA, has been earmarked as a potential RTT therapeutic target.[87] When assessing transcriptome diversity in NDD models, it is important to note the caveats associated with techniques like microarray and RNA sequencing (RNA-seq) analysis, which sometimes interfere with RNA integrity during sample processing and often capture expression of abundant RNAs, where lncRNA expression may be relatively lower. Dysregulated lncRNA expression in combination with functional associations with specific NDD etiologies (e.g., for RTT) may, however, help stratify NDD diagnosis.

Psychological and other conditions

circRNAs and lncRNAs are enriched in cells of the CNS[97,98] and have been implicated in development of neuropsychiatric and psychological conditions. For example, *BDNF-AS* was recently found to be

elevated in postmortem amygdalae of patients with early-onset alcohol use disorder. *BDNF-AS* is thought to decrease *BDNF* expression via recruitment of EZH2, which adds H3K27 trimethyl marks to repress target genes.[99] Additionally, multiple circRNAs are dysregulated in whole-blood samples of patients with major depressive disorder, and these circRNAs are enriched in neuronal pathways.[100] Building on evidence that several lncRNAs are implicated in inflammation, angiogenesis, and apoptosis in stroke models,[101] one ongoing clinical trial is investigating the diagnostic potential of lncRNAs for detection and prognosis of acute ischemic stroke (ClinicalTrials.gov: NCT04175691).

lncRNAs as biomarkers: Empirical evidence

The association of several lncRNAs with ND, cancer, NDD, and psychiatric conditions raises the question of whether they could serve as biomarkers in neuropathological contexts, particularly for diagnosis. A biomarker is specific to the disease in question, can be sampled noninvasively, and is sensitive to early and rapid detection. Biomarkers should help stratify disease risk and prognosis, provide insight into the biological mechanism of disease, and vary in response to treatment.[102] Many of the lncRNAs mentioned above have been used as biomarkers under these criteria using minimally invasive methods. *In vivo*, transcriptomic analysis of plasma-derived cell-free circulating RNAs has revealed *BACE1-AS* to be a diagnostic marker of AD in patients with varying levels of symptom progression.[103] Detection of lncRNA biomarkers from the bloodstream at sites distal to the brain has also been conducted in other NDs with relatively high specificity and sensitivity and, in some cases, has been validated by imaging data and tissue biopsies.[104–112]

While potentially informative, assaying lncRNA expression via the bloodstream requires isolation of serum, plasma, leukocytes, and/or exosomes (because circulating lncRNAs enter the bloodstream packaged in extracellular vesicles or attached to proteins[113]) and may not be completely representative of molecular changes native to the CNS. Liquid biopsies relying on CSF, which contacts the CNS, have been used to identify lncRNA signatures for diagnosis and preventative surgery in a variety of CNS pathologies.[114–116] Although these techniques are promising, relying on circulating lncRNAs as biomarkers for CNS disorders is complicated. Canonically, qRT-PCR is used to assay circulating lncRNA expression; however, there is currently no established reference gene set for lncRNAs from different sources (e.g., plasma versus serum versus CSF). Additionally, lncRNAs may be expressed at low levels (and, thus, difficult to sample), depending on the cell type, and the expression of many lncRNAs is not specifically dysregulated in one disorder. For example, *NEAT1* expression is aberrant in PD, AD, and ALS.[117] For this reason, liquid biopsies for detection of lncRNA biomarkers could be used to supplement existing diagnostic methods rather than as a definitive diagnosis on their own.

lncRNAs AS THERAPEUTIC TARGETS: METHODS, UPDATES, AND REMAINING QUESTIONS

Beyond their potential use as biomarkers, lncRNAs have been investigated as therapeutic targets *in vivo*. Many approaches aimed at developing human therapies utilize RNA-based methods that target lncRNA transcripts for degradation or interference. Currently, 11 RNA therapies are approved by the US Food and Drug Administration (FDA) and/or the European Medicines Agency (EMA); of these, only one, nusinersen, aimed at improving spinal muscular atrophy outcomes, is targeted to the CNS via intrathecal administration (the rest target other tissue types[86]). Most therapies approved for clinical use are either antisense oligonucleotides (ASOs) or siRNAs. ASOs are single-stranded DNA molecules that are designed to be complementary to a target RNA sequence. When bound to the RNA, ASOs inhibit translation, trigger RNase H cleavage of the transcript, and/or interfere with *cis*-splicing elements, leading to exon exclusion.[118] Therefore, the transcript is rendered loss of function. By contrast, siRNAs, which are short single- or double-stranded RNA sequences, take advantage of the endogenous microRNA (miRNA) machinery to cleave target RNAs or recruit repressive proteins. When introduced into the cell, siRNAs load target RNA onto the RNA-induced silencing complex (RISC), which can deadenylate and degrade and/or inhibit translation of the target RNA.

Currently, there are no approved RNA therapies for targeting lncRNA molecules in humans. Many approaches exist to target lncRNA expression in the laboratory, including transcriptional or post-transcriptional inhibition, steric hindrance of secondary structure assembly or effector protein interaction, genome editing, and exogenous introduction of lncRNAs. The efficacy of the approach depends in large part on the lncRNA genomic architecture and structure of the transcript.[119] One approach that has shown promising results for degradation of natural antisense transcripts (NATs) in the CNS *in vivo* is use of ASOs. Modified ASOs that decrease NAT expression (AntagoNATs) have been shown to de-repress transcription of the gene encoding *BDNF* while increasing neuronal outgrowth.[120] These ASOs also upregulate wild-type sodium voltage-gated channel alpha subunit 1 (*SCN1A*) gene expression, which undergoes heterozygous loss-of-function mutations in Dravet syndrome, a rare genetic brain disorder characterized by lifelong epilepsy.[121] Similarly, AntagoNAT-mediated reduction of *UBE3A-AS*, which silences the paternal copy of the ubiquitin protein ligase E3A gene (*UBE3A*), ameliorates cognitive deficits in murine models of the NDD Angelman syndrome[122] (Figures 4A–4C).

Certain lncRNAs have neuroprotective or restorative effects, and it may be useful to upregulate their expression in disease models. For example, glial cell-derived neurotrophic factor (*GDNF*) promotes dopaminergic neuron survival and could ameliorate PD symptoms. SINEUPs, a class of antisense lncRNAs containing repetitive short interspersed nuclear elements (SINEs), promote translation of sense coding mRNAs and can be used to activate protein production. Indeed, adeno-associated virus 9 (AAV9)-mediated delivery of *GDNF*-targeting SINEUPs in the mouse striatum increases endogenous GDNF protein and dopaminergic potentiation while reducing motor deficits and neurodegeneration[123] (Figure 4D). SINEUPs were originally identified in the mouse,[124] and, to date, the number of functionally validated endogenous SINEUP lncRNAs in human

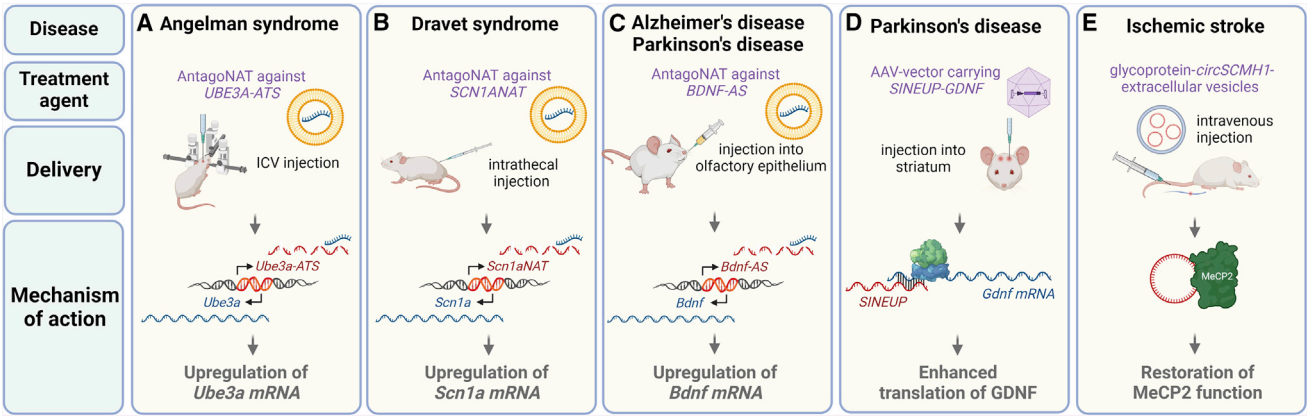

Figure 4. Examples of lncRNAs as potential therapeutic targets in preclinical models of CNS diseases

(A–C) Liposomal delivery of antagoNATs may be used to target lncRNA genes associated with disease. (A) In Angelman syndrome, deficiencies in the maternal allele of the *UBE3A* gene can be compensated by unsilencing the normally imprinted paternal allele. This is achieved by ASO-mediated downregulation of the antisense *UBE3A-ATS* transcript, a negative regulator of the sense transcript. In mouse, intracerebroventricular (i.c.v.) injection of ASOs via antagoNAT delivery partially restores UBE3A protein levels and ameliorates cognitive deficits associated with the disease.[122] (B) Dravet syndrome is caused by heterozygous mutations in the voltage-gated sodium channel gene *SCN1A*. Use of antagoNATs against the antisense transcript *SCN1ANAT* promotes upregulation of *SCN1A* and improves the seizure phenotype in mice.[121] (C) Targeting of the antisense *BDNF-AS* transcript with antagoNATs produces upregulation of *BDNF* mRNA, with therapeutic impact on a number of neurodegenerative disorders like AD and PD. Recently, a direct transnasal delivery method has been proposed that delivers the therapeutic agent directly to the olfactory submucosal space, thus enhancing CNS distribution with a minimally invasive strategy.[127] (D) Antisense transcripts that partially overlap and promote translation of target mRNAs (SINEUPs) have been employed to upregulate GDNF protein levels and rescue motor deficits and neurodegeneration in mouse models of PD.[123] Targeting can be localized via striatal injection. (E) Systemic delivery may also be accomplished intravenously, as in the case of the circRNA *SCMH1* in the form of glycoprotein-*circSCMH1* extracellular vesicles, which improve functional recovery after ischemic stroke in mice and nonhuman primate ischemic stroke models. Mechanistically, *circSCMH1* binds to MeCP2 protein, thereby upregulating transcription of downstream genes involved in brain functions.[133] This figure was created with BioRender.

cells is very limited.[125] While their presence in the human brain transcriptome is uncertain, SINEUPs have a unique mode of action that may inspire biotechnological advances aimed at recovering the physiological levels of a target protein.[126]

Although ncRNAs have been considered for therapeutic targeting in several tissue types and diseases, the CNS poses unique challenges. First, the therapy must cross the BBB, which often necessitates direct intrathecal CNS administration or intracerebroventricular injection, both of which can be risky procedures. Recently, minimally invasive nasal depot (MIND), a topical intranasal method, has been shown to successfully deliver antagoNATs against *BDNF-AS* into the mouse brain[127] via the olfactory submucosal space. Additionally, combination of nucleotide therapies with liposomes has been shown to enhance BBB penetration.[128] Therapies must also be able to cross the cell membrane, be cell subtype and sequence specific with low off-target effects (at the transcriptome and cellular levels), and show low toxicity and immunogenicity. circRNAs are particularly interesting with respect to the last category because they are less immunogenic than other synthetic molecules[129] and can act as miRNA sponges[130] that induce continuous loss of miRNA function. Given the abundance of circRNAs in the brain[131] and their implications in several CNS-related diseases,[132] it will be interesting to follow their use in therapeutic development.

One solution to BBB and cell membrane crossing as well as toxicity and immunogenicity is use of exosomes and other membrane vesicles as therapeutic vehicles. Indeed, delivery of glycoprotein-*circSCMH1* via extracellular vesicle intravenous injection has been shown to improve functional recovery and neuronal plasticity in mice with distal middle cerebral artery occlusions with no report of associated toxicity or immune response[133] (Figure 4E). Exosomes are also a consideration for PD therapy.[134] Combined with novel sequencing methods and emerging functional characterizations of lncRNAs in the CNS, these techniques may bring about substantial advancements in cell- and disease-type-specific ncRNA therapeutic targeting.

SUMMARY

Investigation of lncRNA functions in the CNS is a rapidly expanding field that holds exciting potential for new advances in understanding brain cell physiology and improving disease diagnosis and therapy. This review summarizes important evidence regarding the roles of lncRNAs in brain cellular and molecular processes, highlighting a few lncRNAs that have been studied as biomarkers of CNS disorders involving neurodegeneration, neurodevelopment, and more. Our current understanding is that lncRNAs have a fine-tuning influence in a variety of human diseases and represent a type of molecule that can be easily targeted with high specificity. However, direct involvement of lncRNAs in brain pathologies has been shown for only a reduced number of cases. Given that CNS tissues exhibit large enrichment and diversity of ncRNAs, future research will be key to elucidating the roles of known and still unidentified lncRNAs in the CNS, expanding the potential of these noncodings to serve as diagnostic biomarkers and even targets for treatment of CNS conditions.

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AUTHOR CONTRIBUTIONS

T.S. and S.G. conceived the review topic. T.S., C.M., C.O.-M., and S.G. wrote the entire article and edited it collaboratively.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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