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The history and function of a circular RNA

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Cdr1as/ciRS-7 is a circular RNA conserved in mammals and highly expressed in brain. It features a large number of microRNA target sites bound in vivo by miR-7/miR-671. Cdr1as regulates synaptic activity under stress in a temporal, spatial, and neuron-specific manner. We review genetic, molecular, evolutionary, and physiological data to discuss how Cdr1as and its interactors form a functionally important network of non-coding RNAs that regulates neuronal adaptability. We provide a framework to explore potential roles of other non-coding RNA networks on brain function and their diagnostic and therapeutic potential.

In 2024, the Nobel Prize in Physiology or Medicine was awarded to Victor Ambros and Gary Ruvkun for the discovery of microRNAs (miRNAs), acknowledging their important role as post-transcriptional regulators of gene expression[1–3]. miRNAs are small non-coding RNAs (20–24 nucleotides) that bind 3′-untranslated regions (UTRs) of mRNAs, inhibiting translation or inducing degradation[4–8], primarily via complementarity in their 'seed' region (6–8 nucleotides)[5,6]. Each mammalian miRNA has hundreds of functional targets[9,10], and these target sites are under negative selection in human populations, indicating their significance for human health[11].

Mature miRNAs are processed from longer RNA precursors, first in the nucleus and then in the cytoplasm, by conserved protein machineries and function as a single-stranded RNA within an effector complex[12]. While, perfect complementarity results in the slicing of the target, similar to small interfering RNAs (siRNAs)[13,14], extensive but incomplete complementarity can trigger target-directed miRNA degradation (TDMD)[15–19]. The latest remains poorly understood. miRNA expression and activity are cell-type specific[20], and loss of function experiments have proven their importance as gene regulators across biological systems[21–25].

Another major class of regulatory transcripts are long non-coding RNAs (lncRNAs), which regulate gene expression through interactions with proteins and/or other nucleic acids in different cellular compartments[26,27]. A subclass of lncRNAs are circular RNAs (circRNAs), first observed in the '70 s through electron microscopy in eukaryotic cells[28].

Although circRNAs in animals[29–32] were occasionally described in the 1990s[33–36], only in 2012 and 2013 several groups demonstrated that circRNAs constitute a large class of animal RNAs[37–39]. Canonically, circRNAs are generated through back-splicing of an mRNA precursor transcribed by Poll II. These back-splicing reactions are promoted by reverse complementary sequences in bracketing introns[40]. Numerous circRNAs are evolutionary conserved and enriched in brain[41]. They display exceptional stability due to their covalently closed structure, making them attractive biomarker candidates[42].

Despite growing interest in circRNAs as disease biomarkers, including depression[43], cancer, and cardiovascular conditions[44], studies proposing functional roles of circRNAs in brain remain limited[38,45–53]. Some examples are: the role of CDR1as in the brain[38,47]; the role of circHomer1 during neuronal plasticity[46] and its effects on neurotransmitter pathways[53]; circSLC45A4 as regulator of neural progenitor cells[48]; the role of circSatb1 during dendritic morphogenesis in epilepsy[49]; the role of circFAT3 in regulation of neural development[50]; the function of circMbl in tissue-specific physiology[51]; and the regulatory network of circDlc1(2) that controls glutamatergic signaling in the striatum[52]. Technical challenges, including low expression levels, overlap with host transcripts, and difficulties in achieving specific loss- and gain-of-function, have complicated functional studies. These

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issues are addressed in guidelines for circRNA research by Nielsen et al.[44].

One notable exception is the mammalian circRNA CDR1as/Cirs-7, discovered by the Kjems lab in 2011[54]. It contains an unusually large number of binding sites for a deeply conserved miRNA, miR-7[38,45], and undergoes highly efficient back-splicing. It directly interacts with miR-7 to regulate glutamate release in neurons, particularly during stress[55,56]. CDR1as is further embedded in a regulatory network with the lncRNA Cyrano. While CDR1as regulates miR-7 targeting, Cyrano promotes miR-7 degradation via a highly complementary TDMD interaction[57,58]. This is the only non-coding RNA network in the brain with a partially understood pathophysiological role. Beyond neuronal roles, CDR1as has also been implicated in cancer and stem cell regulation [Box 1].

In this review, we will summarize 15 years of work on CDR1as-centered network and integrate new data on its evolution, expression, and function in placental mammals. These analyses will also critically contextualize the numerous studies proposing circRNA-miRNA interactions which were inspired by the original discoveries of CDR1as and miR-7[38,45,54].

CDR1AS/CIRS-7

Cdr1as, also known as ciRS-7, is a mono-exonic circular RNA[54] highly conserved among placental mammals (Fig. 1A). It is generated through back-splicing from a precursor transcribed from the opposite strand of the cerebellar degeneration-related protein 1 (CDR1) gene on the X chromosome (Fig. 1B). Early studies linked the Cdr1 locus to paraneoplastic cerebellar degeneration, a neurological autoimmune condition[59–61]. However, recent analysis of stranded RNA-seq, ChIP-seq, and CAGE determined that transcripts originating from this locus are derived from the opposite strand: (Cdr1as), and do not produce detectable Cdr1 transcripts in any of the mouse or human brain tissue studied[38,47,54]. Despite this, expression of Cdr1 mRNA under specific conditions cannot be ruled out. The larger transcriptional unit that generates Cdr1as, annotated as LINC00632 (in humans) or Cdr1os (in mice), undergoes highly efficient back-splicing to form a covalently closed circular RNA (Cdr1as/ciRS-7) of 1485 nucleotides in humans and 2975 in mice[54] (Fig. 1C). This back-splicing relies on mammalian-specific flanking elements[62] (Fig. 1B), and achieves near-complete circularization efficiency, making Cdr1as detectable exclusively in circular form, with no linear counterpart[38,45,47,54].

Cdr1as is strongly enriched in the brain, reaching expression levels of constitutive genes[38,45] and increases during neuronal differentiation and maturation[41,50,63]. In the adult forebrain, RNA fluorescence in situ hybridization (FISH) showed that Cdr1as is neuron-specific, with no expression observed in glial cells[47] (Fig. 1D).

Since Cdr1as sequence contains stretches of adenosines, it is, albeit with low efficiency, detected by mis-priming in single-cell or spatial omics experiments that target polyadenine (poly(A)) tails. A comprehensive computational analysis using all publicly available atlases, including the Human Cell Atlas collections released up to 2024, the Human Adult Brain Cell Atlas[64], the Mouse Brain Cell Atlas (mousebrain.org[65]), and Tabula Muris (Tabula Muris Consortium 2018, 2020), revealed that its expression in non-nervous tissues, such as mouse kidney, liver or mucosa, is extremely low. The functional consequences of this low-level expression remain unclear.

Initial functional insights of Cdr1as came from the phenotypical analysis of zebrafish, which lack Cdr1as. Exogenous expression of human Cdr1as in the zebrafish brain was sufficient to alter development, suggesting an in vivo function[38]. Further investigations into Cdr1as's function revealed a complex network of direct and indirect interactions with various non-coding RNAs, including two microRNAs and a long non-coding RNA.

In mice, Cdr1as contains approximately 130 binding sites for miR-7, while over 70 in the shorter human transcript, with more than 60 of these sites conserved across vertebrates[38,45] (Fig. 1C). These sites, corresponding to 6–8 nucleotide seed matches, are distributed throughout the circRNA and were initially predicted using AGO2-CLIP data[38,45]. Direct in vivo biding was later confirmed by mRNA:miRNA chimera analyses, in mouse and human brain datasets[47,66–68], where Cdr1as emerged as the transcript with the highest number of miR-7 chimeric reads, followed by Cyrano.

BOX 1

Role of CDR1AS in cancer and stemness

Numerous studies have reported CDR1as being upregulated in various cancers (reviewed in Zou et al.[155]), where it has generally been proposed to function as an oncogene, primarily through its ability to sequester the tumor-suppressive miR-7. Consequently, it has been associated with poor prognosis across these various cancer types[155].

However, recent findings challenge this prevailing view. Kristensen et al.[156] showed that CDR1as is not expressed within cancer cells of several classical oncogene-driven adenocarcinomas[156]. Instead, elevated CDR1as levels in tumor samples originate from its abundant expression in stromal cells within the tumor microenvironment. Given that a high proportion of stromal cells itself is an independent prognostic factor in adenocarcinomas, such as those originating in the colon, breast, and lung, the correlation between CDR1as expression and poor outcomes may reflect stromal content, rather than a direct oncogenic role.

Additionally, observed correlations between CDR1as expression and the expression of miR-7 target genes may also be explained by varying tumor-to-stroma ratios, rather than direct miR-7 regulation in cancer cells. Adding complexity, Hanniford et al.[157] reported that CDR1as undergoes epigenetic silencing in melanoma cells, a process that promotes melanoma cell invasion and metastasis. This suggests a potential tumor-suppressive role for CDR1as in specific cancer types, opposing its previously described oncogenic function.

Together, these findings highlight the context-dependent nature of CDR1as, also in cancer biology, questioning its universal role as an miR-7 regulator and emphasizing the need to consider cell type-specific expression patterns and tumor microenvironment when evaluating its function across various tissues.

Beyond its involvement in cancer, CDR1as has also been implicated in maintaining the stemness in non-neuronal tissues. In periodontal ligament stem cells CDR1as can act as a regulator for miR-7, leading to the upregulation of Krüppel-like factor 4 (KLF4), a key pluripotency regulator[158]. Potentially through a similar mechanism, it has been reported that CDR1as knockdown in mesenchymal stem cells derived from human umbilical cord leads to downregulation of stemness-associated transcription factors and impaired osteogenesis potential[159]. Additionally, in situ RNA detection has shown that CDR1as is predominantly localized in the epidermal stem cell layer of human skin, suggesting that it may play a similar role in another adult stem cell populations[160,161].

Taken together, these findings further emphasize the multifunctional and context-dependent roles of CDR1as, reinforcing the necessity for nuanced evaluation in both cancer biology and stem cell research.

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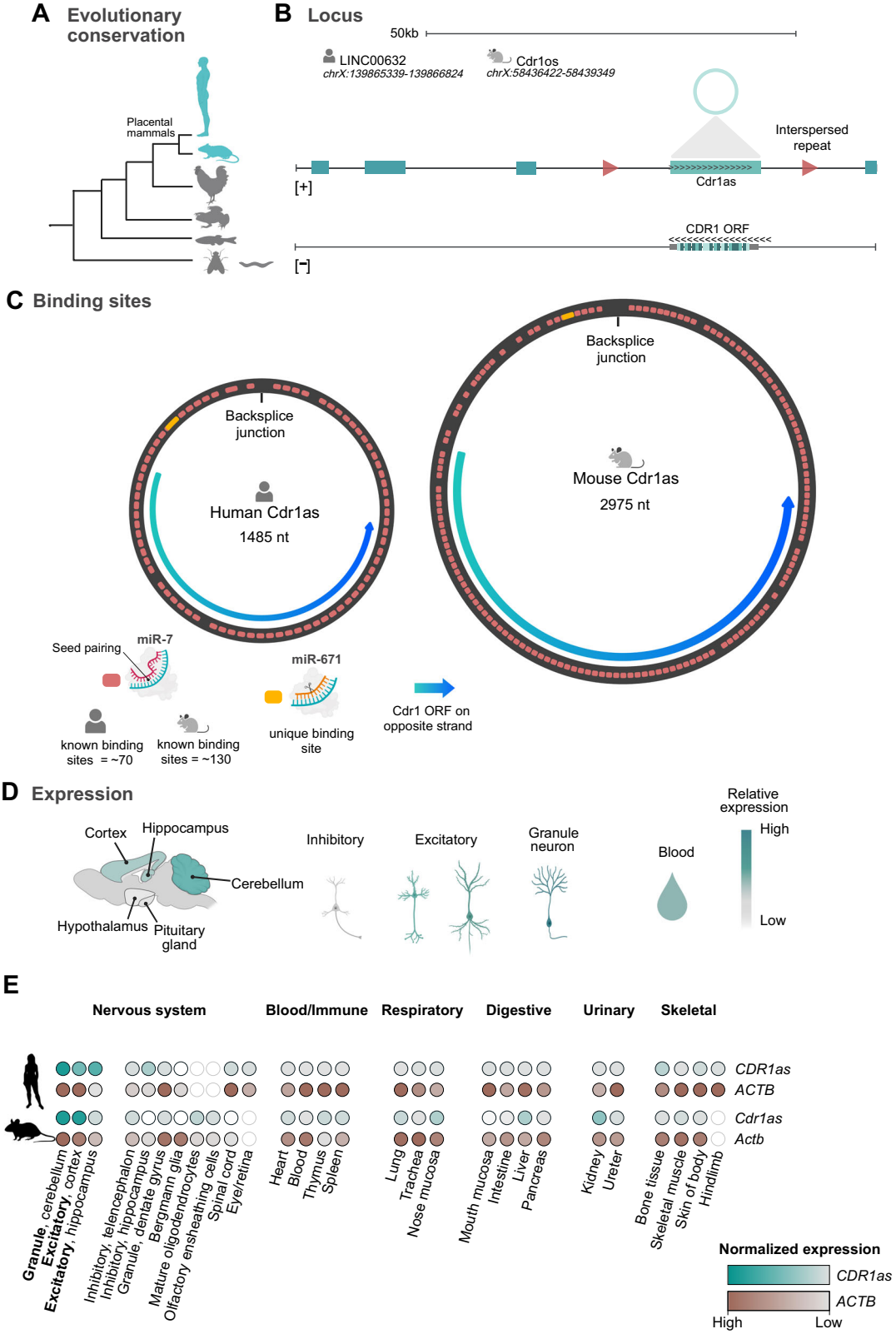

More recently, some miR-7 sites within Cdr1as have been proposed to exhibit architectures compatible with TDMD[69], although the functional relevance of these sites remains unresolved.

Absolute copy numbers of the network molecules per neuron have been estimated for (1) primary cortical neurons, using quantitative single molecule FISH method[56]: miR-7 = avg. 40 molecules per cell; Cdr1as = avg. 262 molecules per cell; Cyrano = avg. 73 molecules per cell and for (2) primary granular cerebellar neurons, using absolute RT-qPCR[58]: miR-7 = avg. 40 molecules per cell; Cdr1as = avg. 146 molecules per cell; Cyrano = avg. 102 molecules per cell. This stoichiometry of the Cdr1as:miR-7 interaction, ranging from 70:1 in humans to 130:1 in mice, suggested that Cdr1as may function as a regulator of miR-7 and its mRNA targets through unknown decoy mechanisms such as a storage, sorter, or localizer of miRNAs, and RNA-binding proteins (RBPs)[38,45].

Fig. 1 | Genomic organization and expression of Cdr1as. A Evolutionary conservation of Cdr1as/Cirs-7. Phylogeny of several animal groups reflect the expression of Cdr1as/Cirs-7 in placentalia (cyan) versus the absence in other animals (gray). **B** Schematic representation of the Cdr1as/Cirs-7 genomic locus, based on the current state of the art. Precursor transcript in chromosome X: LINC00632 (human) / Cdr1os (mouse). Described: Cdr1as/Cirs-7-containing exon in positive strand and Cdr1 open reading frame in negative strand[54] (cyan). Mammalian-wide interspersed repeats required for circularization[62] (red). **C** Cdr1as/Cirs-7 RNA molecular structure in human (1485 nt) and mouse (2975 nt). Described: miR-7 binding sites[38,45] (red), unique miR-671 binding site[54] (yellow), open reading frame on the opposite strand (blue, Cdr1). **D** Relative RNA expression of Cdr1as/Cirs-7 across cells and tissues. Indicated is the relative expression of the back-splice junction across samples from high (cyan) to low (gray). Left: brain region specific[41,45,47] (cortex, hippocampus, hypothalamus, pituitary gland). Middle: neuronal-type specific[47] (inhibitory, excitatory, granular). Right: Human Blood[42]. **E** Normalized abundance of the Cdr1as back-splice junction sequences across matched human and mouse organ systems (nervous, blood/immune, respiratory, digestive, urinary and skeletal). Expression was estimated from raw reads by counting exact k-mer matches to the probe sequences in each single-cell or spatial dataset (Rajewsky lab, unpublished sequence-search index). Values are scaled to the total number of informative k-mers per cell and sample. Expression units are species-normalized pseudocounts (scaled per 10^6 k-mers per cell). Within the nervous system, the same approach resolves region- and cell-type–specific patterns for neuronal and glial subclasses of human[64] and mouse[65]. Datasets: Human Cell Atlas single-cell collections released up to 2024; Human Adult Brain Cell Atlas[64]; Mouse Brain Cell Atlas[65]; Tabula Muris (Tabula Muris Consortium 2018, 2020). Created in BioRender. https://BioRender.com/mdvz52d.

Consistent with this, genetic ablation of the Cdr1as locus in mice revealed a stabilizing effect of Cdr1as on mature miR-7[47]. Further research demonstrated a dynamic feedback relationship, in which miR-7 levels influence the subcellular localization of Cdr1as, linking RNA abundance to spatial regulation within neurons, complicating the understanding of the interactions between these two molecules[55,56,58].

In addition to miR-7, Cdr1as features a single conserved site with near-perfect complementarity for miR-671[54] (Fig. 1C). This unique site, similar to the one utilized by siRNA for gene silencing, enables AGO2-mediated slicing of Cdr1as, representing the first identified degradation mechanism specific to a circular RNA[54]. Initially, miR-671-mediated slicing was thought to occur only in the nucleus, due to the abundance of miR-671 in nuclear compartments[54], however, it is now understood that Cdr1as is enriched in the cytoplasm. In the brain, miR-671-mediated slicing accounts only partially for Cdr1as turnover[58] as in the context of a Cdr1as knockdown, abolishing miR-671 slicing (mutation of binding site) only partially rescue Cdr1as expression[58]. Moreover, the upregulation of miR-7 enhances miR-671-directed slicing of Cdr1as[58]. This dependency on miR-7 suggests an unknown mechanism involving the cooperative action of miR-7 facilitated by binding sites in close proximity[70]. Notably, stress-induced changes in Cdr1as and miR-7 are not accompanied by corresponding changes in miR-671 expression, pointing to context-dependent degradation mechanisms that may operate independently of miR-671 abundance[55,56].

Over the past decade, more than 2,500 articles (Scopus search: *TITLE-ABS-KEY ("circular rna" sponge AND microrna) AND (LIMIT-TO (DOCTYPE, "ar")*) have proposed circRNAs with one or few miRNAs binding sites as regulators of gene expression through sponge-like mechanisms. However, most of these circRNAs are unlikely to fulfill the quantitative requirements for significant regulatory impact[71]. In contrast, the exceptionally high expression of Cdr1as, combined with the large number of miR-7 binding sites sets a unique context for regulatory interactions unlikely to be applicable to most circRNAs.

CircRNA-miRNA regulation is governed by stoichiometry, defined by the absolute abundance of the regulator and number and affinity of available miRNA binding sites[71]. Quantitative modeling shows that miRNA:target regulation operates in a competitive regime, where thousands of endogenous binding sites coexist. Only regulators providing a very large number of high-affinity sites or achieving high local concentrations can substantially alter miRNA activity[71]. Said conditions are rarely met by typical linear mRNAs and are achieved only in exceptional cases such as CDR1as, which combines unusually high, activity-modulated expression in neurons with dozens of conserved miR-7 sites. These constraints may be relaxed only when interacting RNAs are highly locally confined, as in polarized cells like neurons[71]. Outside of restricted cellular compartments, caution is required when interpreting circRNAs with few miRNA binding sites as functionally equivalent to Cdr1as.

miR-7

The most prominent interaction partner of Cdr1as is miR-7, an evolutionarily conserved microRNA originating in bilaterians. In most animals, miR-7 is generated from a single copy within the last intron of the hnRNPK gene. In vertebrates, miR-7 typically exists as four paralogs, following whole-genome duplication events[72]. Although a complete miR-7 loss is rare, it has been reported in a nematode lineage[73–75] (*C. elegans*; Mirgenedb.org). Importantly, also the non-seed part of the mature miR-7 sequence is highly conserved, suggesting multiple evolutionary constraints (Fig. 2A).

In mammals, miR-7 is transcribed from three independently regulated genomic loci (Fig. 2B). In humans, pri-miR-7-1 is co-transcribed with hnRNPK, while pri-miR-7-2 is encoded in an intergenic region, and pri-mir-7-3 is embedded in an intron of a non-coding transcript (MIR7-3HG). In rodents, the first two loci generate the same mature sequence, miR-7a-1 and miR-7a-2. However, the third locus, pri-miR-7b, differs by a single nucleotide in the mature sequence outside the seed region, and might exhibit distinct affinities through secondary binding. These pairing differences affect its interaction with targets, conferring functional diversity[76,77] (Fig. 2C). Remarkably, miR-7 and miR-671 share nearly identical seed sequences, differing only at the sixth position, while diverging substantially at their 3′ ends (Fig. 2C). (April 2025: Mirgenedb.org).

The presence of multiple miR-7 independent loci underscores the need for precise regulation of its mature sequence[78] (Fig. 2B). Although increased seed pairing is generally associated with stronger miRNA-mediated repression (from 6-mer to 8-mer; Fig. 2C), in vitro studies indicate that miR-7 does not follow this linear increase in effectiveness. Most inhibitory effect on miR-7 targets are minimal for most 6-mer and 7-mer pairings, showing target repression with log2 fold change (log2FC) of only 0.1 to 0.2[77].

Consistent with the evolutionary histories of neuronal and endocrine lineages[79,80], miR-7 expression is largely restricted the central nervous system[54,81–83], neuroendocrine glands[84,85], and endocrine pancreatic tissue[86–88] (Fig. 2D). This tissue specificity reflects both the transcriptional and post-transcriptional regulatory events of its precursor molecules[83,89]. For example, during endocrine differentiation, the three miR-7 loci are transcriptionally regulated, resulting in a dynamic expression as cells transition from fetal to adult stages[90–92]. Post-transcriptional upregulation of miR-7 was shown in mammalian cells upon knockdown of the RNA binding protein Human antigen R (HUR)[89]. Subsequent studies revealed that miR-7 is enriched in neurons due to inhibition of its biogenesis in non-neuronal cells, which is mediated by HUR and Musashi RNA Binding Protein 2 (MSI2), in humans and mice[83]. Moreover, miR-7 exhibits differential expression across neuronal subtypes, particularly between inhibitory and excitatory neurons[93] (Fig. 2D).

A key post-transcriptional regulation of miR-7 is its destruction via TDMD mediated by lncRNA Cyrano (OIP5-AS1) and disruption of

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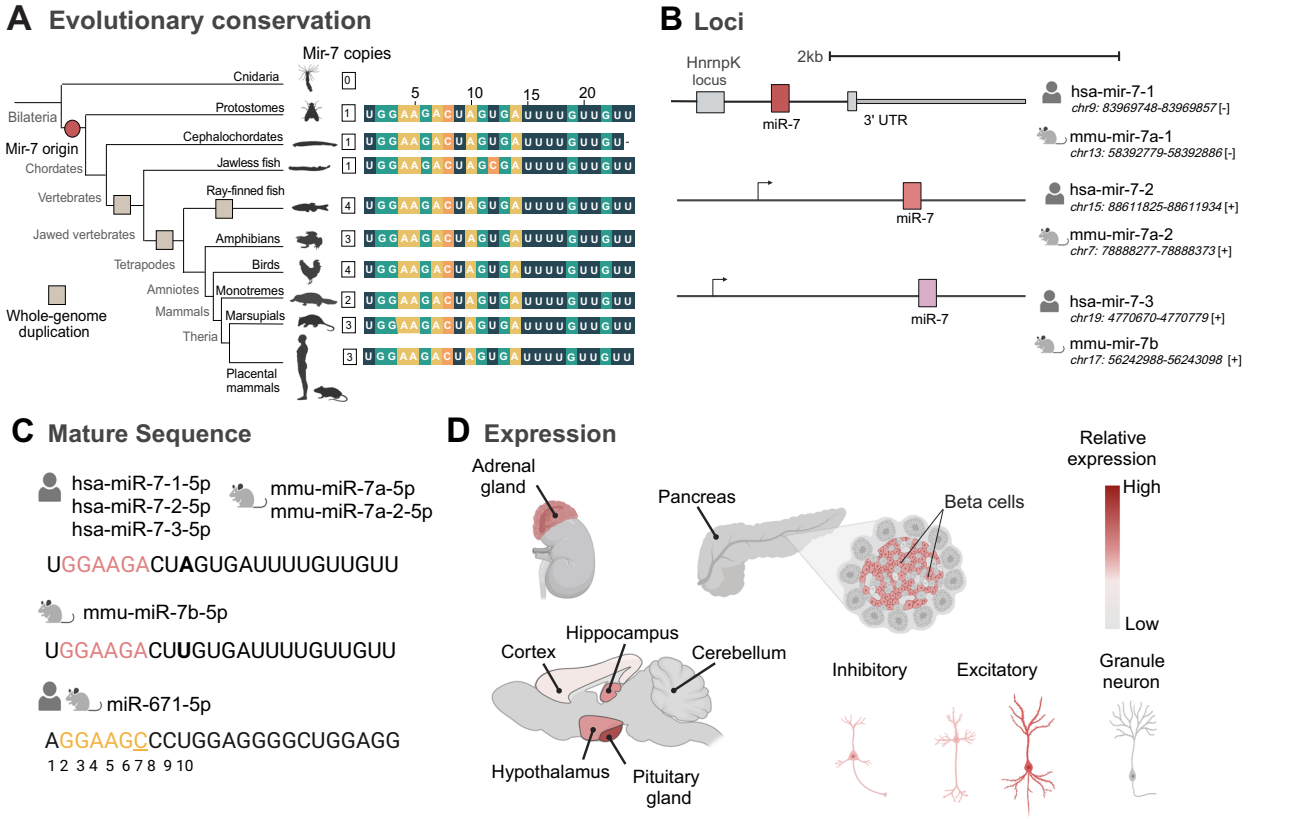

Fig. 2 | Evolution, loci, and expression of miR-7. A Evolutionary tree illustrates the conservation history of mir-7. Left: Phylogeny of several animal groups reflecting the expression of miR-7 in Bilateria, coinciding with the development of the central nervous system. Right: nucleotide conservation of the full mature sequence of miR-7 compared across species. **B** Schematic representation of the three genomic loci of miR-7 in mouse and human. **C** miR-7-5p and miR-671-5p mature RNA sequences comparison. All isoforms expressed in human and mouse. Seed-binding sequence: 2-8 nt (miR-7: red; miR-671: orange). miR-7a and -7b variation in the 10th nucleotide between human and mouse indicated in bold. miR671-5p seed sequence (orange) differs from miR-7 (red) only in the sixth nucleotide (mismatch underlined). **D** Relative RNA expression of miR-7 across cells and tissues. Indicated is the relative expression of the mature miRNA across samples from high (dark red) to low (gray). Left: brain region specific[45,82] (cortex, hippocampus, hypothalamus, pituitary gland). Right: pancreatic beta cells[88]. Middle: neuronal-type specific[93] (inhibitory, excitatory, granular). Created in BioRender. https://BioRender.com/200tks8.

the TDMD machinery results in robust upregulation of both mature miR-7 isoforms across tissues[19].

Initial functional studies in flies identified miR-7 as a regulator of the Notch signaling pathway[94,95], an essential driver of brain development[96]. Although all the functional roles of miR-7 in the mammalian brain are yet to be discovered, studies have demonstrated its role in neurodevelopment and neuronal fate. miR-7 controls cortical progenitor cell expansion, neuronal survival, and brain size through its interaction with Gli3 pathway[97,98], and by regulating Pax6-dependent spatial patterning of dopaminergic neurons[99].

Beyond the nervous system, miR-7 plays essential roles in endocrine physiology. Single-locus knockout models revealed that loss of miR-7a-2 causes sterility due to pituitary dysfunction[100], while inducible deletion of all miR-7 loci confirmed its central role in the hypothalamus, where it is the most highly expressed miRNA[101]. In metabolic contexts, miR-7 controls weight and energy balance by regulating mRNAs involved in melanocortin pathways[102], effect independent of the expression of Cdr1as and Cyrano.

CYRANO/OIP5-AS1

Within the complex Cdr1as-miR-7 interplay, the long non-coding RNA Cyrano (also known as OIP5-AS1 in humans and Oip5os1 in mice) serves as an additional regulator of miR-7 expression. The third exon of this lncRNA harbors a single binding site for miR-7, exhibiting near-perfect complementarity[57] (Fig. 3A), which is conserved from human to zebrafish, but absent in other vertebrate lineages, like sharks[103] (Fig. 3B). In the mouse brain this interaction leads to post-transcriptional degradation of miR-7 through TDMD, as mutating this binding site results in a 10-fold upregulation of miR-7[58]. Cyrano also induces the tailing and trimming of miR-7, although these modifications seem to be unrelated to the TDMD mechanism[58]. Like many lncRNAs, Cyrano's primary sequence (over 8 kb in mice) is poorly conserved. However, several elements of the transcript, including the miR-7 binding site, and other potentially regulatory elements such as: miR-25/92 and miR-153 binding sites, Rbfox site, or poly(A) site, are preserved across multiple species[103]. This suggests a functional importance for these elements, although the exact reasons remain unknown.

Cyrano was first identified in zebrafish, where morpholino-based knockdown studies suggested roles in brain and eye development[57]. However, this phenotype was later deemed likely non-specific, as CRISPR/Cas9 mutants of Cyrano in zebrafish[104] and mice[58] showed no developmental defects or impairments in the adult. Moreover, these phenotypes were induced when injecting morpholino targeting Cyrano RNA in Cyrano KO zebrafish, strongly suggesting that the observed phenotypes were morpholino artifacts[104]. In humans, Cyrano has been implicated in regulating cell proliferation in a miR-7 independent manner by acting as a decoy for the RNA-binding protein HUR[105]. Conversely, in mice, Cyrano has been proposed to influence embryonic stem cell self-renewal through its interaction with miR-7[106]. However, this effect on pluripotency is not observed in Cyrano-depleted human stem cells, which still retain the ability to differentiate into all germ layers[107]. This discrepancy highlights the limited

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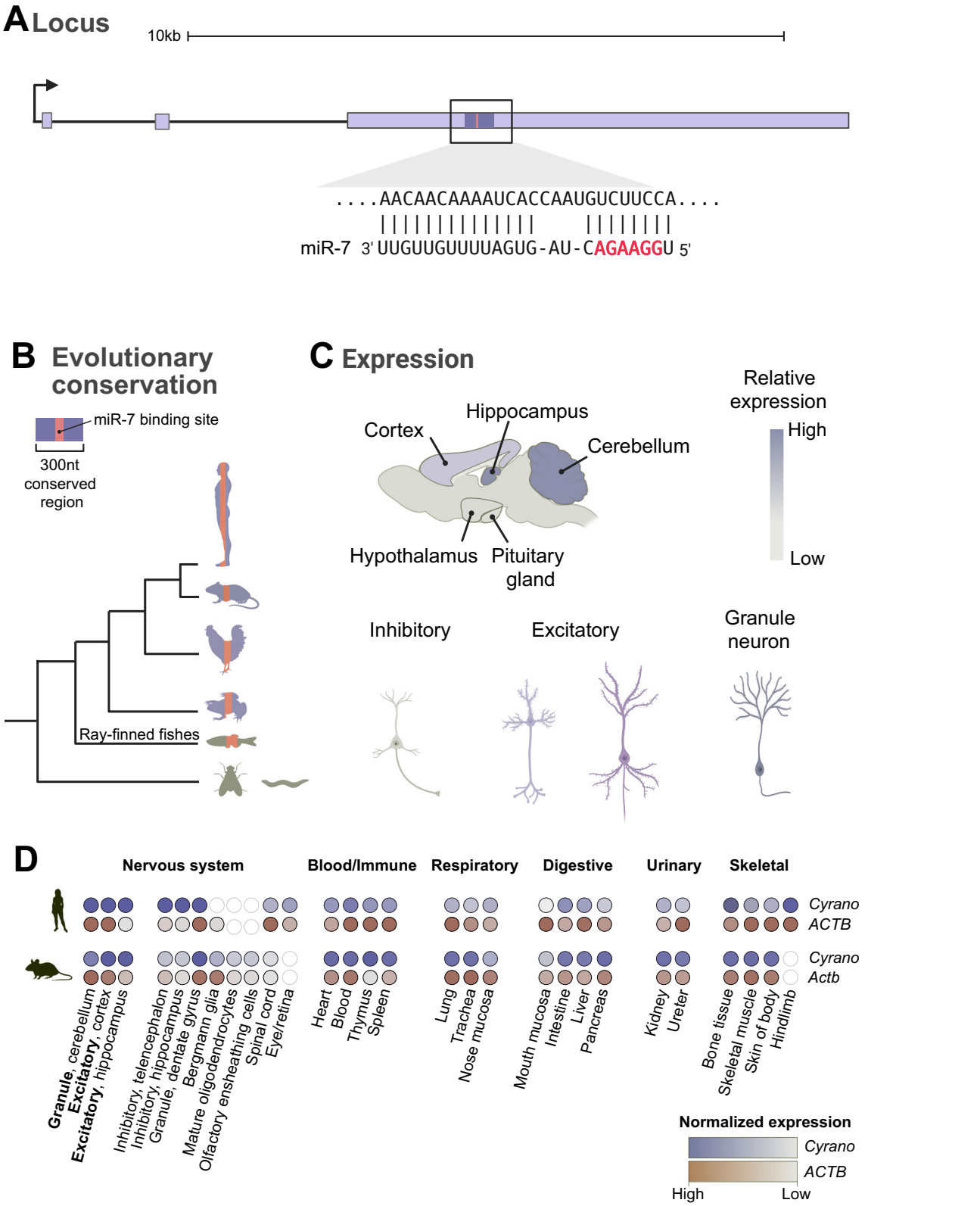

understanding of how Cyrano regulates cell proliferation across species and suggests it may play redundant, indirect, or context-dependent roles that require clarification through targeted rescue experiments.

Given its high expression in the brain (Fig. 3C), Cyrano is the second most enriched miR-7 interactor in mouse brain AGO-CLIP and chimera analyses[47,67,68]. However, in AGO-CLIP data specifically from excitatory pyramidal neurons, Cyrano scores as one of the weakest interactors of miR-7, suggesting heterogeneity in miR-7 binding across different brain cell types[55]. Nevertheless, the number of AGO2-CLIP reads may not linearly reflect binding affinity, as ligation efficiency is influenced by RNA abundance and structure.

Using all available single-cell atlases, including the Human Cell Atlas (collections released up to 2024), the Human Adult Brain Cell

Fig. 3 | Structure, conservation, and expression of Cyrano. A Schematic representation of the genomic locus of lncRNA Cyrano/OIP5-AS1. Exon 3 contains a single miR-7 perfect complementarity site (pink), which triggers miR-7 TDMD. Additionally, one of the several Cyrano conserved regions, a 300nt sequence (purple) flanking the miR-7 biding site emerged in vertebrates from Xenopus to Human, but is not present in zebrafish[57]. **B** Evolutionary conservation of lncRNA Cyrano/OIP5-AS1. Phylogeny of several animal groups reflecting the expression of Cyrano/OIP5-AS1 from zebrafish to human. Conservation of 300nt sequence (purple) containing miR-7 biding site (red). **C** Relative RNA expression of lncRNA Cyrano/OIP5-AS1 across cells and tissues. Indicated is the relative expression of Cyrano across samples from high (purple) to low (gray) Left: brain region specific (cortex, hippocampus, hypothalamus, pituitary gland; Allen Brain Atlas). Middle: neuronal-type specific[65] (inhibitory, excitatory, granular). **D** Normalized abundance of the Cyrano sequences across matched human and mouse organ systems (nervous, blood/immune, respiratory, digestive, urinary and skeletal). Expression was estimated from raw reads by counting exact k-mer matches to the probe sequences in each single-cell or spatial dataset (Rajewsky lab, unpublished sequence-search index). Values are scaled to the total number of informative k-mers per cell and sample. Expression units are species-normalized pseudocounts (scaled per 10^6 k-mers per cell). Within the nervous system, the same approach resolves region- and cell-type–specific patterns for neuronal and glial subclasses of human[64] and mouse[65]. Datasets: Human Cell Atlas single-cell collections released up to 2024; Human Adult Brain Cell Atlas[64]; Mouse Brain Cell Atlas[65]; Tabula Muris (Tabula Muris Consortium 2018, 2020). Created in BioRender. https://BioRender.com/3it2qak.

Atlas[64], the Mouse Brain Cell Atlas (mousebrain.org[65]), and Tabula Muris (Tabula Muris Consortium 2018, 2020), we observed that Cyrano is broadly expressed across both neural and non-neural tissues in mice and humans. Within the nervous system, Cyrano expression is particularly enriched in the spinal cord and excitatory neurons of the hippocampus and cerebellum, compared to inhibitory neurons, glial cells, or retinal cells. Notably, Cyrano expression levels appear consistently higher in all mouse tissues relative to their human counterparts, with particularly elevated levels in the mouse pancreas and lung (Fig. 3D). Functional studies in Cyrano knockout animals demonstrated a specific increase in mature miR-7 levels, that in turn prevented the accumulation of Cdr1as in the neuronal soma[58].

Changes in both predicted and validated targets of miR-7 were predominantly observed in specific tissues and brain regions where miR-7 was constitutively expressed at higher levels, such as the pituitary gland and striatum-thalamus[58]. Incidentally, these regions exhibit lower Cdr1as levels than the cerebral cortex[41,47,54]. This adds to the complexity of miR-7 regulation by its interactors and strongly suggests that an additional layer of regulation might exist, influenced by cell types and cellular contexts.

Cdr1as-dependentRNA network in physiological conditions

Cdr1as molecular interaction partners were first identified over a decade ago[38,45,54]. However, their relationships and role within the brain remained unresolved until independent KO animal models for the Cdr1as locus and Cyrano became available[47,58] (Fig. 4A).

Piwecka et al.[47] generated a constitutive KO mouse model of the Cdr1as locus, the first mammalian KO of a circRNA. This model uncovered an interplay between Cdr1as and mature miR-7/miR-671 stability. Total and small RNA-sequencing showed that Cdr1as deletion reduces mature miR-7 post-transcriptionally across cortex, hippocampus, cerebellum, and olfactory bulb[47]. In the cerebellum, where baseline miR-7 is lower but detectable (Fig. 2D), this decrease is modest yet consistent, supporting a stabilizing role of Cdr1as on miR-7.

The main brain-specific molecular consequence of disrupted Cdr1as:miR-7 interaction appears to be the alteration of immediate early genes (IEGs), the primary activity-dependent responders to neuronal stress, activation or depolarization[108–111]. Several IEGs are known to be direct targets of miR-7 via their 3'UTRs[112–115], and accordingly, IEGs, such as *Fos*, *Jun*, and *Egr*, were upregulated in Cdr1as KO animals. This is accompanied by increased in spontaneous neuronal activation[47] and altered behavioral responses, including impaired reactions to external cues, as assessed by prepulse-inhibition test[116]. Together, these findings established a physiological role for a circRNA:miRNA interaction (Cdr1as:miR-7) in mammalian brain function, and proposed its involvement in balancing inhibitory and excitatory neuronal signaling[47]. However, given the limited number of molecular studies available, additional mechanisms may yet be discovered.

Complementarily, the Cyrano KO animal model generated by Kleaveland et al.[58] provided evidence for an indirect link between Cyrano and Cdr1as. Loss of Cyrano increases miR-7 levels, which in turn destabilize Cdr1as. Strikingly, in these animals, Cdr1as and miR-7 were the only affected transcripts, with no detectable functional or behavioral impairment. In contrast, the KO of Cdr1as alone[47] was not sufficient to alter the expression of Cyrano. Together, both models suggest that Cdr1as might protect miR-7 from Cyrano-mediated TDMD.

Moreover, both studies provided additional insight into miR-671-mediated Cdr1as degradation. In Piwecka et al.[47] Cdr1as KO caused a post-transcriptional stabilization of miR-671, the sole known mediator of Cdr1as turnover[54]. Kleaveland et al. further explored this feedback by mutating the miR-671 site in the Cdr1as sequence and crossing these mice with Cyrano KO animals, partially rescuing circRNA decay while increasing miR-671 levels. Together, these independent findings support the hypothesis of a complex negative feedback loop between Cdr1as and miR-671.

The miR-7/Cdr1as/Cyrano interplay also involves RNA localization dynamics. Cdr1as co-localize within synaptic compartments[56] and is detected in synaptoneurosomes preparations[41]. Elevated miR-7 levels, either following Cyrano loss[58] or exogenous miR-7 overexpression[56], promote Cdr1as sequestration within neuronal soma, whereas under physiological conditions the Cdr1as:miR-7 complex is homogeneously distributed along neuronal projections[56], suggesting a role in modulating synaptic functions. Consistently, selective Cdr1as knock-down (KD) in the cortical neuronal processes reduces both miR-7a and -7b levels and impairs memory extinction[117]. Altogether, these observations by three independent studies, underscore the importance of miR-7:Cdr1as interaction in synaptic regulation.

This body of work delineates distinct roles for these non-coding RNAs in regulating brain function and reveal a complex network of interlinked feedback loops. Only recently the functional advantages of such intricate circuitry in the mammalian brain began to be understood.

Molecular network during stress

Recent studies demonstrated that various neuronal stressors, including oxidative and metabolic insults, excitotoxicity, and synaptic hyperactivation, induce coordinated and time-dependent endogenous changes in the Cdr1as/miR-7/Cyrano network (Fig. 4B, C). For instance, Scoyni et al.[55] used oxygen–glucose deprivation (OGD) in mouse cortical neurons to simulate ischemic conditions and observed significant Cdr1as downregulation under stress, accompanied by transcriptional upregulation of miR-7 and consequent downregulation of its target genes. Cyrano, was also showed significantly downregulated, consistent with elevated miR-7 levels.

Further investigations revealed time-dependent dynamics within this regulatory network. Both Cdr1as and Cyrano, were downregulated 6 h post-OGD. Although miR-7 initially decreased at 6 h, the releases from regulatory effects of Cdr1as and Cyrano became evident at 12 h post-OGD, coinciding with miR-7 upregulation. The initial miR-7 downregulation is consistent with mature miR-7 post-transcriptional

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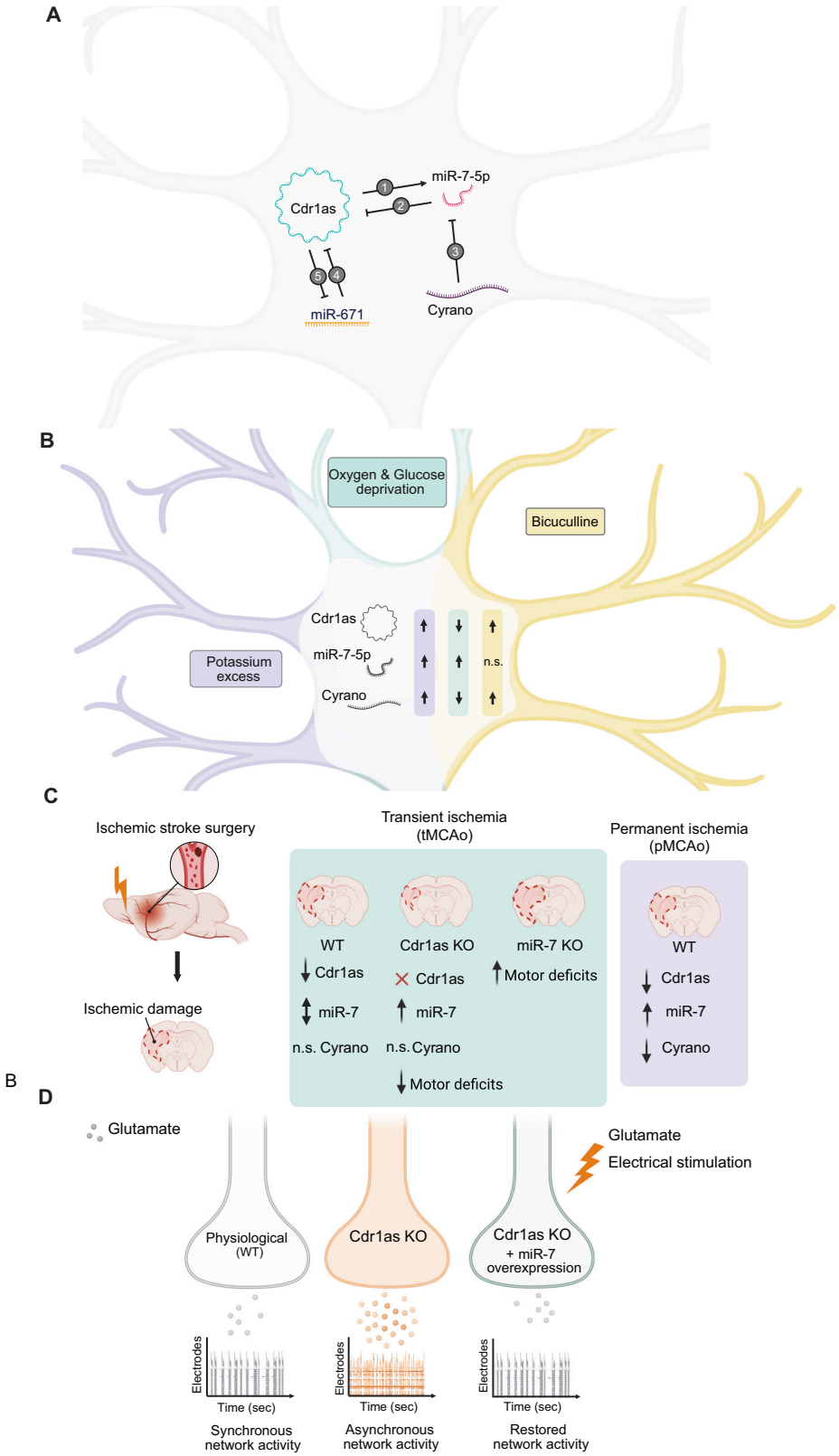

stabilization by Cdr1as, whereas the later miR-7 rebound resulted from increased miR-7 transcription combined with the diminishing of both its regulators. Notably, OGD triggered similar responses in both WT and Cdr1as KO neurons, suggesting an additional regulatory loop within the network that function independently of Cdr1as expression. This raises the hypothesis that individual network components might be regulated autonomously[55] (Fig. 4B).

In vivo studies further underscored context-dependent responses to ischemic stress within the network. In a permanent middle cerebral artery occlusion model (pMCAO)[118], mirroring the in vitro OGD paradigm, Cdr1as and Cyrano expression was reduced, with concomitant increases in miR-7, consistent with the in vitro findings. In contrast, transient MCAO (tMCAO)[119], a clinically relevant model that includes reperfusion injury[120], showed acute Cdr1as downregulation

Fig. 4 | The Cdr1as/miR-7/Cyrano regulatory network. A Schematic representation of the dynamic molecular regulatory network involving Cdr1as/Cirs-7, miR-7, Cyrano, and miR-671 in neurons. Cdr1as directly interacts with miR-7 molecules[38,45]. Complete KO of Cdr1as/Cirs-7 destabilized miR-7 post-transcriptionally[47]. Direct or indirect upregulation of miR-7 downregulates expression of Cdr1as[55,56,58]. lncRNA Cyrano triggers degradation miR-7 molecules through a TDMD mechanism[57]. KO of miR-7 site on Cyrano upregulates miR-7 expression[58]. miR-671 destabilized Cdr1as/Cirs-7 by slicing of the circRNA molecule due to high complementarity biding[54,58]. Disruption of miR-671 binding site on Cdr1as/Cirs-7 increase the circRNA and miR-671[58]. Complete KO of Cdr1as/Cirs-7 upregulates miR-671 post-transcriptionally[47]. Created in BioRender. https://BioRender.com/d639swi. **B** Schematic representation of in vitro stressors in forebrain neurons and their proven molecular effects on the network (Cdr1as/Cirs-7, miR-7, Cyrano). Purple: global depolarization by extracellular potassium[56]. Blue: oxygen and glucose deprivation[55]. Yellow: induction of homeostatic plasticity by Bicuculline[56]. Created in BioRender. https://BioRender.com/xwkh5rs. **C** Schematic representation of permanent (pMCAo) and transient (tMCAo) ischemic stroke surgery in mouse brain. Resulting molecular effect on the network (Cdr1as/Cirs-7, miR-7, Cyrano), ischemic lesion size and behavioral changes. In the schematic the ischemic damage in pink and dotted line is representative of the relative lesion size as measured by MRI[55]. Created in BioRender. https://BioRender.com/ijyhduh. **D** Schematic representation of neuronal network activity and glutamate secretion changes upon stress/stimulation in WT and Cdr1as-KO neurons. Left/Gray: physiological glutamate secretion in WT neurons and subsequent synchronous network activity. Middle/Orange: increased glutamate release and asynchronous network activity in Cdr1as-KO neurons[56]. Right/Green: rescue of glutamate secretion and restored network activity in Cdr1as-KO neurons upon miR-7 upregulation after glutamatergic[55] or electrical stimulation[56]. Created in BioRender. https://BioRender.com/jpctgbe.

but variable miR-7 and Cyrano levels[55]. Notably, in Cdr1as KO mice subjected to tMCAO, miR-7 levels were markedly increased, supporting a previously described negative feedback loop[58]. Furthermore, the KO mice displayed reduced ischemic lesions and improved motor performance, suggesting that loss of Cdr1as confers neuroprotection by mitigating neuronal injury, cytokine release, and calcium influx[55] (Fig. 4C).

Independent studies examining the roles of Cdr1as and miR-7 in transient ischemia have yielded diverging results. While Cdr1as is consistently downregulated post-ischemia[121], miR-7 changes remain variable, with reports of both upregulation[122] and downregulation[123]. Notably, both artificial enhancement and inhibition of miR-7 expression have shown beneficial outcomes in experimental stroke models[122,123]. The importance of miR-7 was further supported by miR-7 KO mice studies. Both partial (miR-7a1/miR-7b double knockout)[58] and full miR-7 KO[92] strains exhibited exacerbated neuronal damage and worsened functional outcomes after tMCAO, confirming the critical importance of miR-7 in ischemic neuronal resilience[55,121].

Beyond ischemic and metabolic stressors, Cerda-Jara et al. showed that sustained global depolarization also modulates the regulatory network using excess potassium (K +) in mature primary cortical neurons[124]. Within 15 min, Cdr1as levels increased, mimicking IEGs kinetics, and promoted stabilization of mature miR-7. Conversely, Cyrano displayed a rapid but transient upregulation at 5 min post-depolarization, suggesting distinct temporal dynamics among network components. This activity-dependent regulation was neuron-specific, as K+ treatment failed to modulate the RNA network in astroglia[56] (Fig. 5A). Together, these findings highlight the tight, stimulus-dependent regulation of the Cdr1as/miR-7/Cyrano network across time and depolarization strength[55,56].

Additionally, the direct synaptic relevance of this network was examined by inducing homeostatic plasticity via GABA-A receptor blockade using bicuculline. This treatment increased both Cdr1as and Cyrano levels, while mature miR-7 and its primary transcripts remain unchanged. Remarkably, Cdr1as KO neurons, which exhibit spontaneous hyperactivity[47], did not respond to bicuculline-induced synaptic modulation, suggesting a crucial role for Cdr1as in facilitating synaptic flexibility during homeostatic plasticity.

Taken together complementary in vitroand in vivo data support a context-specific role for the Cdr1as/miR-7/Cyrano network in neuronal stress responses. These findings point to Cdr1as as a key regulator of miR-7, particularly during sustained synaptic remodeling or prolonged ischemic stress, with implications for long-term synaptic plasticity and post-injury recovery.

Glutamatergic regulation in response to neuronal stress

The cellular mechanisms by which Cdr1as/miR-7 regulatory network modulates neuronal activity under stress has been identified (Fig. 4D). In vitro overexpression of miR-7, replicating stress-induced molecular events during neuronal stress, demonstrated that the interaction between Cdr1as and miR-7 regulates glutamatergic signaling, affecting morphology and network activity[55,56].

In cortical neurons, miR-7 overexpression had no effect on glutamate-induced excitability in cells, but significantly reduced glutamate sensitivity in Cdr1as KO neurons, thereby reversing their hyperexcitable phenotype. This effect was specific to glutamatergic signaling, with no detectable changes in GABAergic responses[55]. Consistently, direct measurements of presynaptic glutamate release showed that miR-7 overexpression selectively reduced glutamate secretion in Cdr1as KO neurons, rescuing their aberrant synaptic output, while having no effect in WT neurons[56].

These complementary approaches emphasize that in cortical neurons under conditions of sustained stress, glutamatergic transmission is regulated not by miR-7 levels alone but by the functional interplay between miR-7 and Cdr1as. Therefore, Cdr1as expression determines the magnitude and efficacy of miR-7 activity.

This interaction has pronounced morphological and physiological consequences on neuronal function. miR-7 overexpression in Cdr1as KO neurons increased neurite length, indicating a potential role in regulating neurite outgrowth[55]. Moreover, it rescued impairments in network synchronization, restoring normal levels of spike frequency, burst synchrony, and network oscillations characteristic of advanced synaptic maturation[56].

At the molecular level, these neuronal phenotypes correlate with miR-7-mediated regulation of specific target mRNAs. CLIP-seq analyses in pyramidal excitatory neurons confirmed miR-7 interactions with mRNAs involved in glutamatergic transmission and neuronal projections. Moreover, gene ontology analyses revealed significant enrichment of glutamatergic pathway genes in Cdr1as KO neurons overexpressing miR-7[56]. Notably, several of these targets were previously validated regulators of insulin secretion in pancreatic cells[92], highlighting conserved regulatory mechanisms. Enhanced target repression in these KO neurons by overexpressing miR-7, underscored the buffering role of the Cdr1as-miR-7 interaction in regulating glutamatergic transmission[56].

In summary, after a decade-long molecular characterization, the identification of endogenous triggers uncovered specific cellular and molecular mechanisms through which Cdr1as and miR-7 govern neuron-specific functions. Nevertheless, further research is essential to fully understand these triggers and elucidate their broader implications for human health.

Therapeutic potential

The dynamic landscape of small and long non-coding RNAs has underscored their therapeutic potential across diverse pathological contexts[125,126]. Specifically, circRNAs have recently emerged as promising therapeutic targets[127]. Here, we focus on recent advances in the

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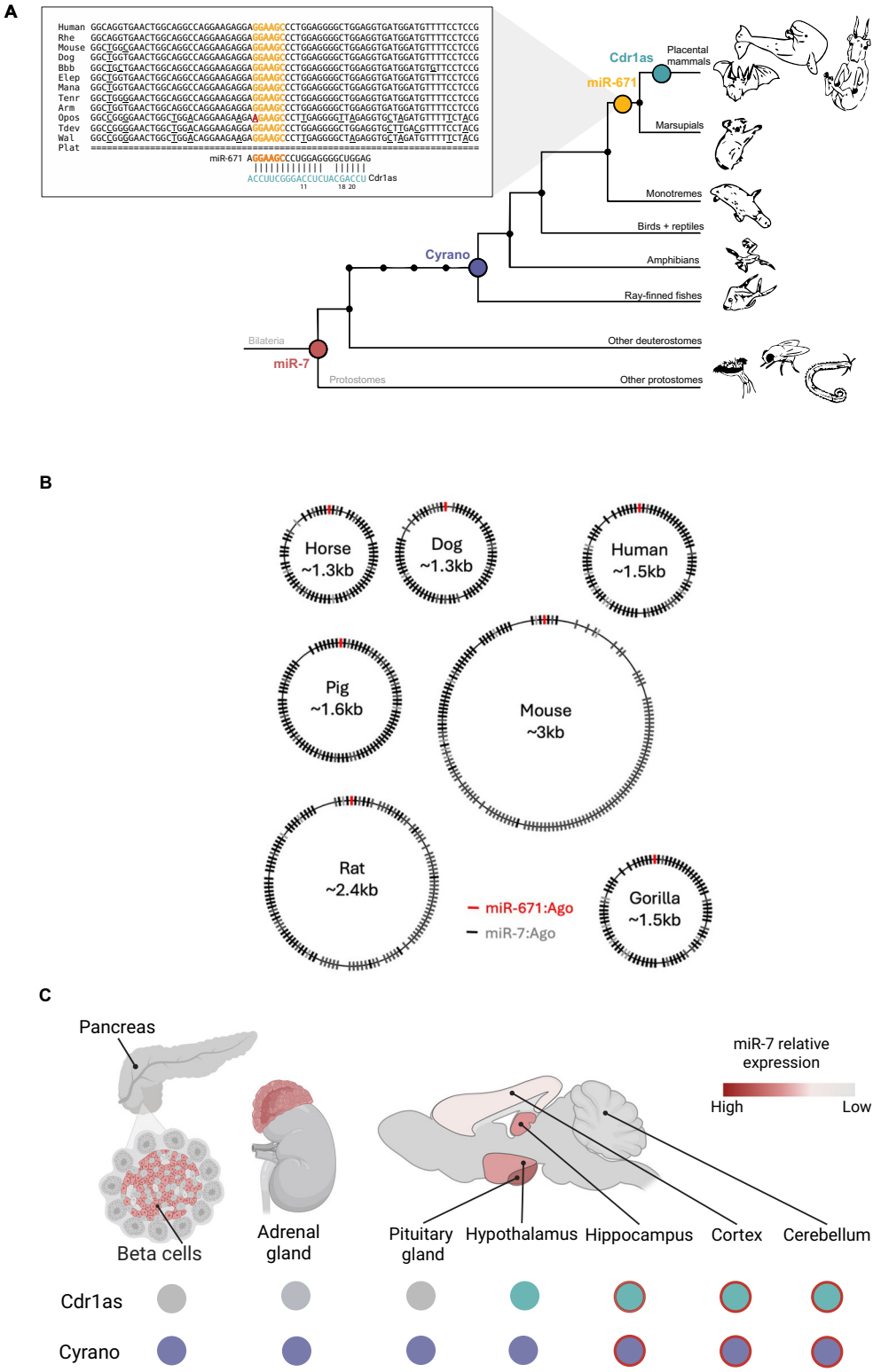

Cdr1as/miR-7 regulatory network that emphasize the spatial, temporal, and cell-specific regulation, laying a foundation for targeted therapeutic interventions in neuronal disorders.

The Cdr1as/miR-7 network regulates glutamatergic signaling, relevant in conditions ranging from ischemic stroke, involving neuronal death, to psychiatric and cognitive disorders characterized by altered neuronal connectivity. These findings indicate that targeting this network may provide therapeutic benefits across diverse neurological conditions.

Recent evidence showing substantial variability in miR-7 regulation during neuronal stress[55,56] highlights its critical role in post-transcriptional control of neuronal survival under excitotoxic conditions and in maintaining synaptic transmission. This positions miR-7 as a promising therapeutic target for disorders associated with neuronal

Fig. 5 | Evolution and tissue-specific activity of the Cdr1as network. **A** Evolutionary emergence of miR-7, Cyrano, miR-671 and Cdr1as/Cirs-7. **B** Schematic representation of Cdr1as/Cirs-7 RNA sequence lengths across several placental mammals. miR-7 (black) and miR-671 (red) binding sites are included. **C** Schematic representation of co-expression gradient of miR-7 and its regulators in different tissues. miR-7 expression is represented by a gradient from deep red (high expression) to gray (low expression) across tissues. Each dot beneath a tissue indicates the expression with Cdr1as (cyan) and Cyrano (purple); gray indicates lack of expression. A red outline around a dot denotes experimentally validated regulatory activity on miR-7 by the regulator. Left: neuroendocrine glands (pancreas, adrenal, pituitary) express high miR-7 and low or absent regulators levels[86–88]. Middle: Hypothalamus express high levels of miR-7 and no functional effects of the regulators[102]. Right: Forebrain (hippocampus, cortex, cerebellum) express high levels of regulators and lower levels of miR-7[54,82,83] consistent with the regulators being functionally active[47,55,56,58]. Created in BioRender. https://BioRender.com/tprxso8.

hyperexcitability and dysfunctional glutamatergic transmission. For instance, disrupted glutamatergic neurotransmission contributes to major depressive disorder, where restoring signaling reverses stress-induced structural brain changes[128]. Similarly, miR-7 upregulation in Cdr1as KO neurons restores cortical glutamatergic transmission[55,56]. More broadly, miR-7-driven regulation of neuronal synchrony may offer therapeutic avenues for disorders affecting network-level dynamics, such as autism spectrum disorder[129,130].

Beyond therapeutic modulation, Cdr1as and miR-7 also hold promise as diagnostic biomarkers,

as both are detectable in human peripheral blood[42]. Given the strong brain specificity of Cdr1as[41], and its limited expression in other tissues[47], its circulating levels likely reflect a brain origin, making it an ideal biomarker for neuropsychiatric conditions. Furthermore, miR-7 is present in multiple extracellular forms, such as free-circulating RNA, Ago2-associated complexes, and extracellular vesicles, supporting its utility as a diagnostic molecular signature across pathologies[131–133].

Importantly, because the Cdr1as/miR-7 network is endogenously regulated by miR-671, targeting miR-671 offers an indirect and precise approach to control Cdr1as and miR-7 levels. Such modulation could function as a temporal switch, enabling acute regulation of Cdr1as and secondary effects on miR-7. This strategy is particularly promising given the recent advances in small-RNAs delivery to the brain[134,135], which enabled clinically approved RNA-based therapies(i.e.,: Onpattro 2018; Givlaari 2019; Oxlumo 2020; Leqvio 2021). Consistently, miRNAs have been explored as therapeutic candidates since their discoveries, with multiple clinical trials attempts over the last decade[136,137].

Discussion

An RNA circuit for spatial and temporal stress control

Neurons experience stress from early development onwards, requiring robust and conserved cellular stress responses[138]. While transcriptional regulation predominantly drives main intracellular reprogramming, post-transcriptional mechanisms enable precise spatial and temporal control, an essential feature for neurons given their sensitivity, non-renewability, and central role in organism-wide responses. In this context, miRNA-mediated post-transcriptional regulation excels in localized, potent regulation during processes like synaptic plasticity[139,140]. Although numerous miRNAs and mRNAs are actively transported to dendrites[141,142], only a subset show activity-dependent induction and translation at synapses[139], emphasizing the role of non-coding RNAs in neural adaptability.

Recent advances have identified a neuron-specific post-transcriptional network of non-coding RNAs: miR-7, Cdr1as, Cyrano, and miR-671[38,45,47,54,58]. This network regulates synaptic transmission upon cellular stress and represents the first mechanistically resolved endogenous RNA-only regulatory circuit[55,56]. The network exploits key properties of non-coding RNAs, including rapid activity bypassing protein translation[27], structural flexibility facilitating simultaneous interactions with diverse biomolecules (proteins, nucleic acids, and lipids)[143]. Furthermore, circRNAs are exceptionally stable due to their covalently closed structures[38,39], while miRNAs, stabilized by RNA-protein complexes, exhibit potent regulatory capacity by targeting multiple mRNAs simultaneously with varying specificity and efficacy[5]. Together, these properties ensure precise, localized, and versatile control of gene expression with Cdr1as, Cyrano and miR-671 dynamically tuning miR-7 activity to ensure accurate glutamatergic signaling in excitatory neurons during significant stress[55,56].

Evolutionary assembly of miR-7 neuronal regulatory loop

Interestingly, the network components emerged at distinct nodes of evolution. miR-7 is the most ancient molecule, originating in bilaterians alongside nervous system centralization[81] and is predominantly expressed in neuro-secretory tissues[84], suggesting an ancestral role in neurosecretion. Conversely, the other components of the network emerged later: Cyrano in the last common ancestor of bony vertebrates, miR-671 in marsupials and placental mammals, and Cdr1as exclusively in placental mammals (Fig. 5A, B).

In light of this stepwise evolutionary emergence, miR-7 likely has two distinct functions. First, it has an ancient developmental role involving cell fate determination conserved across species through the regulation of PAX6 (TargetScan.org), a crucial transcription factor involved in regulating the eye, pancreatic, and neuronal differentiation[144–148]. While this developmental function is well established the involvement of Cdr1as:miR-7 interactions during development remains largely unexplored. Second, miR-7 appears to have acquired a more recent role in regulating (neuro)secretion in glutamatergic neurons and other neurosecretory cells, acting in differentiated, post-developmental tissues. In this context, miR-7 regulation by Cdr1as and its role in stress responses likely reflects later evolutionary adaptations. Overall, miR-7 conservation is primarily driven by its essential developmental role via PAX6, with secretion and stress response regulation representing more recent specialization. A compelling example of the evolutionary emergence of this network is miR-671:Cdr1as relationship, which may represent an evolutionary kernel[149]. The primary transcript of miR-671 originated from a coding exon of the ancient gene CHPF2 which shows characteristic third-position nucleotide wobbling across evolution. His variability ceases in the region encoding the mature miR-671 after the opossum, a marsupial with a primitive placenta. In marsupials, miR-671 sequence accumulated mutations affecting the seed and the 3′ end regions, critical for Ago2-dependent slicing, whereas, in placental mammals, the entire 23-nucleotide mature sequence is strictly conserved, indicating strong purifying selection. This conservation suggests that the functional interaction between miR-671 and its primary target[47], Cdr1as, emerged in placental mammals. The extensive complementarity between miR-671 and Cdr1as likely imposed strong evolutionary constraints, fixing this regulatory module and marking the origin of an evolutionary kernel in the brain.

Combinatorial expression patterns regulate miR-7 activity

In mammalian neurosecretory cells and pancreatic beta cells, which share neuronal-like characteristics[79,80], miR-7 is expressed at notably high levels compared to the cortex[92,150]. It is the most abundant miRNA in the pituitary gland, and pancreas and is also enriched in the hypothalamus.

High miR-7 expression suggests a direct inhibitory role in secretory pathways. When this brake is lifted, secretory RNA targets experience a direct derepression[92]. Notably, miR-7 regulators Cdr1as and Cyrano are either not co-expressed (pancreas, adrenal gland, pituitary gland) or non-reactive to miR-7 perturbation (hypothalamus)[102]. Conversely, in the cortex, hippocampus and

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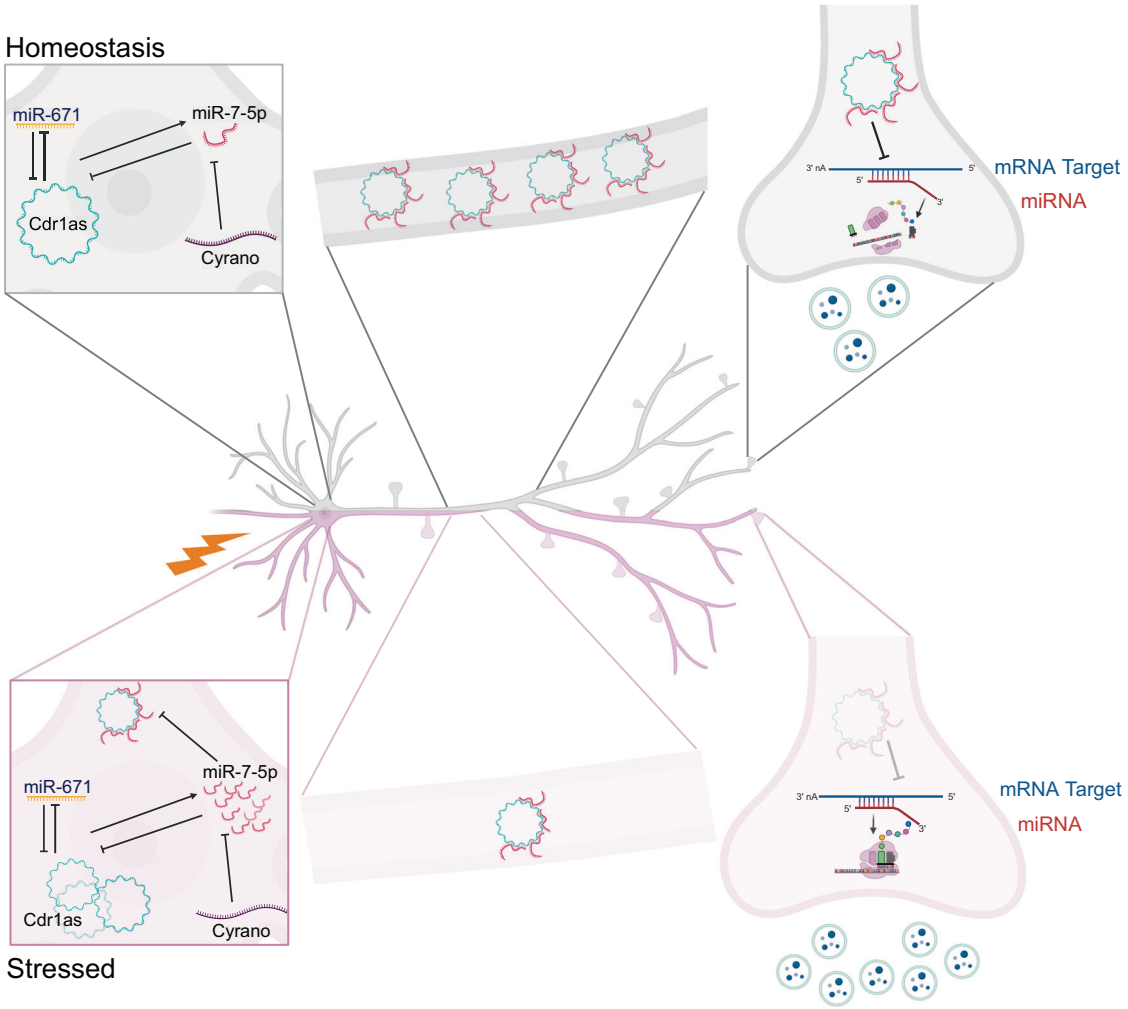

Fig. 6 | A model for stress-dependent miR-7 regulation by Cdr1as. Transport hypothesis: Cdr1as/Cirs-7 act as a molecular transporter, directing miR-7/AGO2 complexes to specific subcellular compartments. Primary stabilizer role of Cdr1as/Cirs-7 on miR-7, relevant during stronger and long-term synaptic changes, where miR-7 levels are sustainably up-regulated. Created in BioRender. https://BioRender.com/4txpco6.

cerebellum, miR-7 expression is low, and tightly regulated by high levels of Cdr1as and Cyrano[47,58]. However, the combinatorial expression of miR-7-Cdr1as-Cyrano within these regions varies across cell types, including excitatory and inhibitory neurons (Tabula Muris and Tabula Sapiens Consortium[65]).

These region- and cell-specific combinatorial expression pattern might dictate the strength and specificity of miR-7-mediated regulation (Fig. 5C). Although KO models demonstrate limited miR-7 impact under basal neuronal conditions[47,58], stress-induced dysregulation of miR-7 strongly impacts glutamatergic transmission[55,56], underscoring the importance of regulatory context in shaping miR-7 function.

Transport hypothesis: Cdr1as guides miR-7 localization

Upon neuronal stress, miR-7 targets mRNAs involved in the glutamatergic signaling[55,56]. Although the mechanisms underlying miR-7 target selection remain unclear, non-random distribution in dendrites and somas[56,58] suggests that Cdr1as may transport miR-7 to specific subcellular compartments (Fig. 6). This transport hypothesis is supported by the local translation within neurites of mRNA targets encoding synaptic vesicles and glutamate receptors[151].

In addition to spatial regulation, the suggested role of Cdr1as-mediated TDMD of miR-7[69] might contribute to its localized turnover, independent of Cyrano. This potential turnover event could be effective due to multiple TDMD sites on Cdr1as compared to Cyrano[69].

The puzzling regulation mediated by miR-671 and Cyrano

Although miR-671 is a known regulator of Cdr1as turnover[54,58], its expression remains remarkably stable during neuronal stress, both in vitro and in vivo[55,56]. In this context, miR-671-mediated slicing would be consistent with the rapid and dynamic post-transcriptional reduction in Cdr1as levels. However, this mechanism alone cannot fully explain Cdr1as turnover. Disruption of the miR-671:Cdr1as interaction only partially rescues Cdr1as expression in the brain, as shown by the incomplete recovery observed in miR-671 binding-site mutants crossed with Cyrano KO animals[58]. In the same study, a miR-7-mediated negative feedback on Cdr1as was identified, yet the combined effects of miR-671 slicing and miR-7 feedback still fail to explain the full magnitude of Cdr1as regulation observed in vivo[58].

Adding further complexity, Cdr1as expression is subject to circadian regulation, fluctuating across the light–dark cycle[152]. This suggests an intrinsic baseline rhythm of Cdr1as expression that is independent of neuronal stress and may involve circadian mechanisms.

miR-7 and miR-671 share most of their seed sequence, raising the possibility of overlapping target pools (Fig. 2C) with differing binding affinities due to mismatches in their 3′ region of the miRNAs[76,77].

Whether this sequence similarity enables coordinated regulation or competitive interactions between the two miRNAs remains unknown.

Moreover, Cyrano expression exhibits context-dependent dynamics under neuronal stress, varying with both the strength and duration of the stimulus[55,56]. This multifaceted regulation highlights a critical gap in our understanding: although the molecular roles of miR-671 and Cyrano are relatively well defined, their broader contributions to stress-responsive regulatory networks in neurons remain poorly understood.

Lessons from the Cdr1as network

The Cdr1as/miR-7/Cyrano network provides a rare quantitative framework for understanding how non-coding RNAs can form autonomous regulatory circuits with a precision and robustness typically attributed to protein-based feedback loops. It illustrates that circRNAs can achieve functional significance when expression, binding-site architecture, and cellular localization reach the stoichiometric threshold required to influence microRNA activity. This principle likely extends to other non-coding RNA networks, where quantitative balance, rather than mere presence, defines regulatory potential.

The stepwise evolutionary assembly of this network, from an ancient miR-7 module to the later incorporation of Cyrano, miR-671, and the placental mammal-specific circRNA Cdr1as, illustrates how newly emerged non-coding RNAs can be co-opted into pre-existing pathways to enhance precision in highly specialized cells.

Beyond miRNA sequestration, Cdr1as:miR-7 interaction highlights broader functional possibilities for circRNAs, such as protein binding, translation control, or innate immune interfaces[153,154], etc. These insights argue for mechanistic and context-aware circRNA regulation validations. Using the Cdr1as toolkit as a template, the field could prospect other circRNAs under these constraints, distinguishing rare, high-impact circuits from correlational noise.

Ultimately, the Cdr1as network illustrates how quantitative and spatial control of RNA-RNA interactions enables adaptable, non-protein-based regulatory mechanisms. Integrating single-cell resolution, targeted perturbations, and quantitative modeling will be essential to test and generalize these principles across RNA regulatory networks.

Outlook and outstanding questions

Regulation of the Cdr1as-centered network during neuronal stress involves both transcriptional and post-transcriptional components[55,56], although critical details, remain unexplored.

Cdr1as mechanistic discoveries demonstrated that copy number, binding-site number/affinity, and compartmentalization determine whether a circRNA can meaningfully affect miRNA activity. A key future challenge for the circRNA field will be to establish quantitative approaches to assess these requirements. Integrating absolute molecule counting, miRNA-target chimera quantification, and computational modeling could define the quantitative benchmarks to distinguish exceptional regulators such as Cdr1as, with its dozens of miR-7 sites, from the many circRNAs carrying only a few low-affinity binding sites.

Another relevant unanswered question is the cell-type specificity of the network modulation. miR-7, Cdr1as, and Cyrano show brain-region and cell-type-specific co-expression, with their functional interplay becoming most prominent under stress conditions. Future studies should aim to map active neural network modules where RNA molecules are co-expressed and functional. For example, combining single-cell multi-omics coupled with excitatory versus inhibitory neuronal activity.

Current knowledge of this regulatory network is largely derived from murine models. Sequence length, miR-7 binding-site layout, and cortical circuitry differ across species, raising critical questions regarding its conservation and divergence in human-specific brain functions. Understanding how these mechanisms translate to human physiology and pathophysiology remains crucial for future research. Comparative functional studies across placental mammals (e.g., mouse, rat, human) combined with iPSC-derived neuronal subtypes and brain organoids, could provide an ideal system to investigate species-specific differences in Cdr1as-dependent regulation.

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Author contributions

C.A.C.J. and F.S. conceptualized and wrote the manuscript together, with iterative discussions and input from N.R. and J.K. N.R. led the initial framing of the review and provided extensive conceptual guidance and expertise on the content and figures throughout the development of the manuscript. D.L.P. analyzed the expression of CDR1as and Cyrano across hundreds of thousands of sequenced cells from various tissues. G.Z. performed evolutionary analyses of CDR1as, Cyrano, and miR-7. P.B. conceived and design figure 8 and proofread the manuscript.

Competing interests

The authors declare no competing interests.

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