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REVIEW

MicroRNAs in the neural system

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Abstract Precise spatio-temporal control of gene expression at transcriptional and translational levels is required for both of proper developmental programming of the central nervous system and the performing of normal brain functions. Many studies have demonstrated that microRNAs (miRNAs), a class of endogenous small RNAs, participate in post-transcriptional regulation of gene expression, and thus execute regulatory functions in various biologic processes. Emerging evidence indicates that miRNAs participate in gene regulatory networks during the developmental, physiologic, and pathological processes of the brain. In this review, we attempt to summarize some of the recent advances in research on the involvement of miRNAs in the regulation of neuronal development, neuroplasticity, and brain diseases, revealing their indispensable roles in neural functions.

Keywords MicroRNAs, brain, central nervous system, development, neurological diseases

1 Introduction

The importance of the Nobel-winning microRNA (miRNA) was not fully-noticed until 20 years after its discovery (Ruvkun et al., 2004). Generally speaking, miRNAs are a class of short (19 to 25 nucleotides), single-stranded, non-protein coding RNAs, and they broadly reside in almost all living species, from virus to human, exerting function to repress expression of target genes. Since transcription (miR-29 family, etc.) or released as introns (such as miR-326) (Rodriguez et al., 2004) in the form of primary miRNA, they are spliced into stem-looped precursors by the Drosha and Parsha complex in the nucleus. Then, assisted by Exportin-5, the looped dsRNAs are exported to the cytoplasm, where they are cleaved by Dicer RNase III to produce mature miRNAs (Bernstein et al., 2001). Mature miRNAs are then assembled into an RNA-induced silencing complex (RISC) and can bind the specific site at the 3′ untranslated region (3′UTR) of an mRNA with their seed regions (the 2nd to 8th nucleotide) of the prior strand. The translation of the targeted mRNAs is halted by the degradation of Dicer (RNA splicing protein), or the reversible binding of miRNA (Lee et al., 2002; Cougot et al., 2004). The latter is a more common way of miRNA functioning in vertebrates (Fig. 1).

Up to date, over 700 human miRNAs have been identified (Griffiths-Jones et al., 2008). Bioinformatic and computational analyses predict that a miRNA (such as miR-124) may regulate hundreds even thousands of genes, and up to 30% genes in the genome may be miRNA-regulated (Wienholds and Plasterk, 2005). Accumulating evidence reviews the important roles of specific miRNAs as regulatory switches during development, organogenesis, and cellular differentiation. MiRNAs control distinct functions that are required for the maintenance of each tissue and cell subtype. They are also found to play important roles in cancer development and progression, as well as in other common diseases.

The brain, consisting of neurons and glial cells, is a well-established central dominator of action, motion as well as learning and memory. According to current research, neurons are considered the core components of the nervous system, being electrically excitable cells that process and transmit information by electrochemical signaling via connections with other cells called synapses, while glial cells maintain homeostasis, provide support and protection for the neurons, or even integrate neuronal inputs and release transmitters. These processes and functions require precise control of gene expression, such as neo-protein synthesis during learning and memory (Costa-Mattioli et al., 2009). Yet, due to the complexity of the brain and the neural cells themselves, the mechanisms by which the brain maintains the delicate regulation of developmental and physiologic functions, as well as the causes for cognitional, psychological as well as neurodegenerative diseases are not well understood. However, the importance

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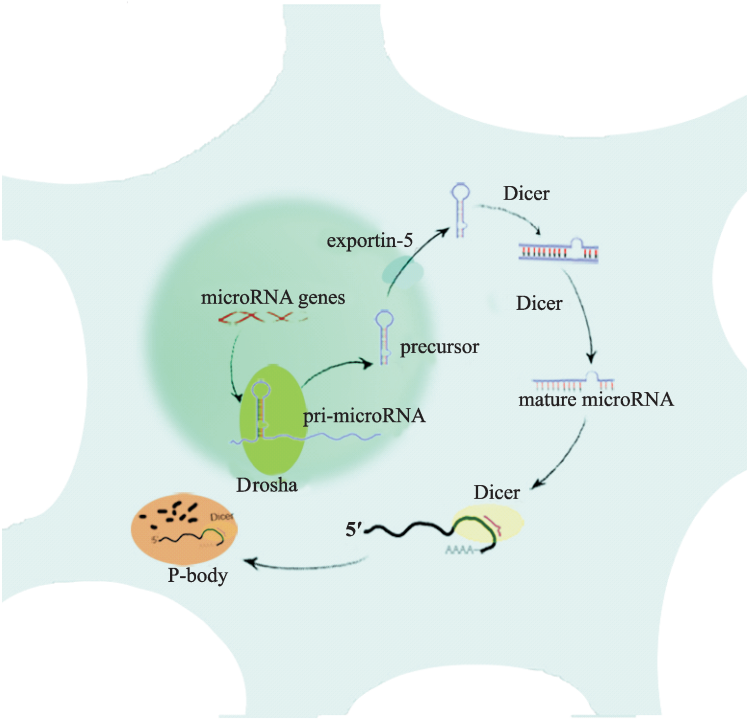

Fig. 1 The production of an microRNA. Since transcripted or released in the form of primary-miRNA, they are spliced by the Drosha and Parsha complex into stem-looped precursors. Then the looped dsRNAs are translocated from the nucleus to the cytoplasm, and processed by Dicer RNase III into small dsRNA fragments (Bernstein et al., 2001). Mature miRNAs, assembled into an RNA-induced silencing complex (RISC), can bind the specific site at 3′UTR of a gene with the seed regions (the 2nd to 8th nucleotide). The translation of their target mRNA sequences is suppressed by degradation (which happens in P bodies), or by reversible binding.

of miRNAs in brain physiology and pathology is increasingly recognized (Fiore et al., 2008). It was observed that knockout of Dicer, the processing enzyme of miRNA, causes abnormal morphogenesis during brain formation and somitogenesis, and this can be rescued by miRNA supplement (Giraldez et al., 2005).

2 MicroRNAs and neuronal development

The development of a neuron from neuro-stem cells to mature ones with dendrites and synapses is a complicated course, which can be divided into three stages: neurogenesis, neural differentiation, and neuronal maturation. During the primary stage, embryonic stem cells grow into neural stem cell precursors. Then the precursors initiate neural differentiation with axons and dendrites (called neurites) budding from the cell body. Functionally mature neurons are formed after neuronal maturation. At all the stages of neural system formation, miRNAs have been shown to exert their power as modulators (Fig. 2).

During neurogenesis, the process in which embryonic stem (ES) cells develop into neural progenitor cells (when cells undergo mitosis), miRNA has been shown to participate in timing and potentiation of each stage (Sempere et al., 2004). Bioinformatic and *in situ* hybridization analysis of the expression profiles of 38 conserved miRNAs in the developing and adult brain of zebrafish indicated that many miRNAs have differential expression profiles in neural cells, such as miR-92b, which has shown restricted expression in neuronal precursors and stem cells; miR-124 is constitutively expressed in mature neurons and is enriched during transition from proliferation to differentiation; while miR-9 exists in both proliferative cells and their differentiated progeny; miR-222 shows regionally restricted expression in telencephalon; and miR-218a is cell-type specifically expressed in motor neurons (Kapsimali et al., 2007). These studies implicate that microRNAs play distinct roles at all developmental processes.

Both microRNA let-7 and lin-4 are heterochronic switch genes temporally controlled to specify the timing of developmental events. Lin-4 RNA, up-regulated at the end of the first larval stage, suppresses Lin-14 and Lin-28 expression levels to allow progression to late larval stages (Feinbaum and Ambros, 1999; Olsen and Ambros, 1999). Reinhart et al. found that during late larval stages, inhibition of let-7 gene activity leads to reiteration of larval cell fates, whereas increase in let-7 gene dosage during larval stages causes premature shift to adult gene expression patterns. The mechanism may involve let-7

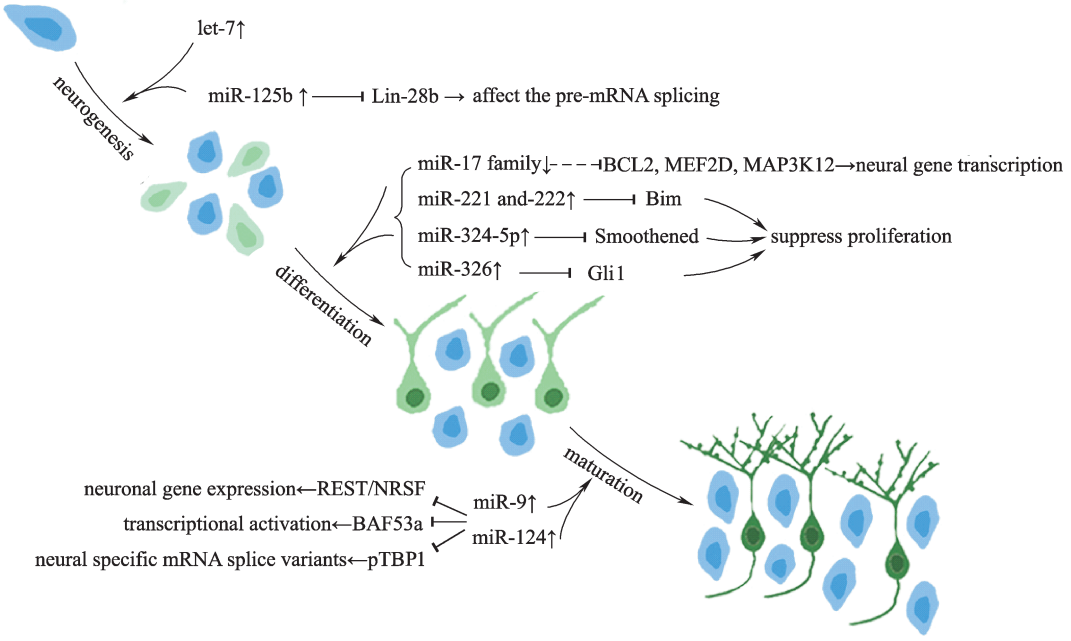

Fig. 2 Regulation of neuronal development by microRNAs. The developmental process from neural progenitor cells to mature neurons involves neurogenesis, differentiation and neuronal maturation. Increasing expression of Let-7 and miR-125b promotes primary neural fate determination in progenitor cells. While miR-221, –222, –324-5p, and –326 inhibit neural progenitor proliferation by suppressing key molecules in nerve growth factor (NGF) and hedgehog (HH) signaling pathway. MiR-9 and –124 are marker miRNAs, affecting neural gene expression and mRNA splicing, during the last stage in neuronal maturation.

targeting 3′UTR of other heterochronic genes, such as *lin-14*, *lin-28*, *lin-41*, *lin-42*, and *daf-12* (Reinhart et al., 2000). As an important class of regulators of gene expression, miRNAs are stringently regulated. An elegant feedback loop is observed between the miRNA and pluripotency factor Lin-28, an RNA binding protein that inhibits the splicing of its target, specially the precursor of let-7 (Rybak et al., 2008). During neurogenesis, increased expression of miR-125b can regulate the feedback loop by targeting 3′UTR of Lin-28 mRNA (Wu and Belasco, 2005).

Sustained increase of miR-221 and −222 regulates a wide variety of cellular functions including neural growth and differentiation in PC12 cells. The increase is induced by activated ERK1/2, a key enzyme in the mitogen-activated protein kinase (MAPK) cascades (Ashraf et al., 2006). One of the identified potential targets downstream is the pro-apoptotic BH3-only protein, Bim, which has been reported to be involved in NGF-dependent survival (Terasawa et al., 2009). In addition, miR-125b, miR-324-5p, and miR-326 target and functionally suppress expression of Smoothened, a G-protein coupled receptor. MiR-324-5p also targets Gli1, a transcription factor, to further regulate HH signaling at a downstream level. This promotes granule cell progenitor differentiation, thereby allows maturation and growth inhibition, and antagonizes the effect induced by Shh (Ferretti et al., 2008). A number of other reports have shown in non-neural systems that miRNAs regulate specific signaling pathways, including MAPK (Thum et al., 2008; Deleault et al., 2008; Paroo et al., 2009), NGF, and Hedgehog (HH)-Gli1 (Thatcher et al., 2007; Eberhart et al., 2008; Friggi-Grelin et al., 2008), which are well-known pathways governing cell proliferation and halting differentiation in the neurons as well.

MiRNAs are also found to promote neuronal maturation. The transcription factor Nerfin-1, required for central nervous system (CNS) axon pathfinding, is transcripted in many neural precursor cells, including all early delaminating CNS neuroblasts, but is post-transcriptionally silenced in most cells. Kuzin et al. detected multiple miRNA binding sites in the 3′UTR of Nerfin-1 and demonstrated that multiple miRNAs targeting different binding sites, but not a single miRNA, are required to block ectopic protein expression in neural precursor cells or to temporally restrict expression in neurons (Kuzin et al., 2007). MiR-9 and -124 are two miRNAs gradually up-regulated during the process of neuronal maturation (Kosik, 2006). It was observed that up-regulated miR-9 and -124 accelerate the process in three distinct ways. (1) They can activate neuronal gene expression by inhibiting transcriptional factor REST/NRSF (RE1 silencing transcription factor), which functions by suppressing neural genes specifically (Visvanathan et al., 2007). (2) MiR-9 and -124 can modulate chromatin structure through suppressing the expression of BAF53a, a component of the BAF complex (Ikura et al., 2000). The BAF complex (loss of BAF53a)

can perturb or relocate the nucleosomes to expose transcriptional factors' binding site by its ATPase activity (Wu et al., 2007; Yoo et al., 2009). (3) Altering pre-mRNA splicing by modulating the expression of pTBP1. PTBP1, a target gene of miR-124, can inhibit the production of neural-dominant mRNA splice variants (Makeyev et al., 2007).

3 MicroRNAs and cerebral functions

Learning and memory as well as circadian regulation are two interesting brain functions being intensively studied. Nudelman et al. showed that environmental stimuli, such as pilocarpine-induced seizures, contextual fear conditioning, cocaine injection, and exposure to odorants, can induce rapid and transient increases of miR-132 expression (Nudelman et al., 2009). A high expression level of miR-132 is induced by cAMP-response element binding protein, a transcription factor involved in the process of learning and memory, and expression of miR-132 in cortical neurons results in neurite outgrowth (Vo et al., 2005).

MiRNAs also regulate spine structure, which is the basis of neuronal structural plasticity and is required for the formation of long-lasting memory. Experiments of Schratt et al. showed that environmental stimulus-induced expression of miR-134 and miR-138 enlarges spine structure by down-regulating cytoskeleton-dynamics-enzyme LIM-domain kinase 1 and acyl protein thioesterase 1 mRNA (Schratt et al., 2006; Siegel et al., 2009), indicating the potential involvement of miRNAs in the modulation of neural plasticity, especially synaptic plasticity, and their association with learning and memory functions of the brain.

Circadian rhythm is an internal clock that keeps one accustomed physiologically and behaviorally to the 24 h day-night shift. The primary circadian clock in mammals is located in the suprachiasmatic nucleus (or nuclei) in the hypothalamus, which receives information about illumination through the eyes, affecting light-related animal behavior (Borrelli et al., 2008). It has been reported that miRNAs participate in the regulation of circadian rhythm. For instance, rhythmic expression of miR-26a in chicken cone photoreceptors regulates the L-type voltage-gated calcium channel alpha1C subunit controlling cock crowing (Shi et al., 2009). CLOCK and BMAL1 are two important transcription factors that induce transcription of circadian rhythm genes at the E box elements within their promoters (Gekakis et al., 1998; Bunger et al., 2000). Cheng et al. showed that miR-219 is a target gene of the CLOCK and BMAL1 complex. MiR-219 shows circadian expression in the suprachiasmatic nucleus. Repression of miR-219 in the brain lengthens the circadian period (Cheng et al., 2007). MiR-132 is induced via an MAPK/CREB-dependent mechanism by photic entrainment cues, modulates the expression of clock-genes, attenuates the entraining effects of light, and in turn affects the wake-sleep cycle. Many circadian rhythms genes, especially *rfx-4* and *scop*, are targets of miR-132 and −219 (Cheng et al., 2007).

4 MicroRNAs and neurological diseases

Disorders in the neurological system include developmental diseases, psychiatric disorders, neurodegenerative diseases, and cancer-related diseases.

Neurodevelopmental disorders occur during infancy, leading to mental retardation, developmental stagnation, etc. (Jellinger, 2003). One example is the Rett syndrome, an X-linked disorder characterized by developmental stagnation, stereotypical movements, microcephaly, seizures, and mental retardation. Rett syndrome is associated with autism and defects in synaptic plasticity. Abnormal expression of methyl-CpG binding protein 2 (MeCP2) may result in the disease. Klein et al. demonstrated that the translation of MeCP2 is under the control of the miR-132 and proposed that miR-132 prevents abnormally high level of MeCP2 during neuronal maturation and the increase of MeCP2 caused by a block of miR-132 function may contribute to Rett-like symptoms observed in the MeCP2 over-expression phenotype (Klein et al., 2007).

Neurodegenerative diseases of the CNS include Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease that are characterized in disordered protein aggregation or loss of dopaminergic neurons. MiRNAs are believed to contribute to the etiology of neurodegenerative diseases. It was found that specific miRNAs, including miR-221/222 and miR-107, show an abnormal expression patterns in AD (Wang et al., 2008; Hebert et al., 2008, 2009; Boissonneault et al., 2009). Some miRNAs, such as miR-298 and miR-328, regulate beta-site amyloid precursor protein-cleaving enzyme 1 (beta-secretase, BACE1) and the amyloid precursor protein (APP) at post-transcriptional level (Boissonneault et al., 2009). AD is caused by plaque aggregation mostly consisting of APP and BACE1 modulates the cleavage of APP. In PD, the expression of miR-7 and miR-8 is down-regulated, affecting the disease in different ways. MiR-7, which is highly expressed in neurons, down regulates α-synuclein and protects cells against oxidative stress (Junn et al., 2009). The miR-8 mutant phenotypes show elevated apoptosis in the brain and behavioral defects (Karres et al., 2007). These findings underline the fact that miRNAs could represent a new tool as biological markers or a new target for pharmacological approaches.

The most common brain tumor is glioma, which arises from glial cells. Interestingly, aberrant miRNA expression patterns were found in this type of cancer cells, indicating a mechanism in tumorigenesis (Silber et al., 2009). Low expression of miR-34a, a transcriptional target of oncogene

p53, promotes glioma cell proliferation and survival, modulating up shift of oncoprotein Notch-1, Notch-2, CDK6, and c-Met in glioma cells (Li et al., 2009). Results of U251 glioma cell lines suggest that miR-221/222 are regulators of tumor suppressor gene p27Kip1, a cell cycle inhibitor, and co-suppression of miR-221/222 expression in advanced gliomas inhibits glioma cell proliferation via a mechanism involving the up-regulation of p27Kip1 (Zhang et al., 2009). It was also demonstrated that the brain-enriched miR-128 is down-regulated in glioma tissues and cell lines. MiR-128 targets to the 3′UTR of E2F3a, a transcription factor that regulates cell cycle progression, and over expression of miR-128 inhibits glioma cell proliferation (Zhang et al., 2009).

Many studies have shown deregulation of miRNAs in pathological conditions, including AD and PD. These reported changes in miRNA expression in various neurological disorders are summarized in Table 1. In addition, accumulating evidence indicates that miRNAs are also potential therapeutic targets for certain brain diseases such as malignant brain cancer. Zhou et al. have reported that down-regulation of miR-21, one of the most frequently over-expressed miRNA in human glioblastoma (GBM) cell line, with a specific antisense oligonucleotide, induces apoptosis and inhibits cell-cycle progression (Zhou et al., 2010). It will not be surprising to see in the coming few years that miRNAs related to brain diseases are being rapidly identified and synthetic mimetics of these

Table 1 MicroRNAs in neural diseases

MicroRNA	expression	references	target	function
Alzheimer's disease				
miR-221/222	↓	Lukiw et al., 2009	survivin-1 homolog BIRC1	
miR-9, 125b, 146a	↑	Sethi and Lukiw, 2009		
miR-107	↓	Wang et al., 2008		May down-regulate BACE1 and accelerate AD.
miR-34a	↑	Wang et al., 2009	BCL2	
miR-20a family (miR-20a, miR-17-5p, miR-106b)	↓	Hoert et al., 2009	APP	Coordinatively regulate APP expression.
The miR-29a/b-1 cluster	↓	Hebert et al., 2008	BACE 1	Contribute to increased BACE1 and Abeta levels in sporadic AD.
miR-128a	↑	Carrettiero et al., 2009	BAG2	Control BAG2 levels physiologically, which can tune paired helical filament Tau levels in neurons.
miR-298, -328		Boissonneault et al., 2009	BACE-1	
Tourette's syndrome				
miR-189		Rodriguez et al., 2004	SLIT-RKT1	
Rett syndrome				
miR-184	↑	Nomura et al., 2008		Down-regulated by MeCP2.
miR-132		Klein et al., 2007	MECP-2	Bind to the 3′-UTR of the MeCP2 mRNA, and prevent deleteriously high MeCP2 levels during development.
Spinocerebellar ataxias				
miR-101, 19, 130		Lee et al., 2008	Ataxin	Lack of Dicer in vertebrate compromises cell viability in various brain regions mediated via coregulation of the ataxin-1 gene by these miRNAs.
Parkinson's disease				
miR-8	↓	Karres et al., 2007		Both up-regulation and down-regulation of miR-8 cause increased neurodegeneration.
miR-133b		Kim et al., 2007	PITX-3	Form a negative feedback loop with the transcription factor Pitx3, and this pathway might be defective in patients suffering from Parkinson's disease.
miR-221/222	↓	Lukiw et al., 2009	survivin-1 homolog BIRC1	
miR-433		Wang et al., 2008	FGF-20	
miR-7	↓	Junn et al., 2009	Synnuclein	
Huntington's disease				
miR-9,9*	↓	Nass et al., 2009	REST CoREST	

(*Continued*)

MicroRNA	expression	references	target	function
Glioma				
miR-221/222	↑	Conti et al., 2009	p27kip1	
miR-128	↓	Zhang et al., 2009	E2F3A BMI1	Inhibit proliferation of glioma cells.
miR-34a	↓	Li et al., 2009	Notch-1, Notch-2, c-Met	Inhibit glioblastoma growth.
miR-21	↑	Zhou et al., 2010	S-TRAIL	Regulate the expression of several tumor suppressor genes. Inhibition of miR-21 in a glioblastoma cell line results in increased apoptosis.

↑: up-regulation; ↓: down-regulation.

miRNAs are being tested for the treatment of certain neurological disorders.

5 Conclusions

The proper function of neural cells and the nervous system involves many key biological processes starting from stem cell differentiation to neuronal outgrowth, guidance and stabilization, transcriptional control of neuronal fate, synaptic target recognition, etc., and requires sophisticated modulation of spatial and temporal expression of concerned genes (Chisholm and Jin, 2005). The phenomenon that miRNA binding can both transiently inactivate and lead to degradation of its target mRNA is not being fully clarified (Nelson et al., 2003). It is noteworthy that miRNAs not only function as down-regulators of their targets, but also serve as fine-tuners (Karres et al., 2007). It has been demonstrated that miR-8 buffers atrophin to the optimal level (Karres et al., 2007) and that Mef2-mediated transcription of the miR-379-410 cluster fine-tunes Pumilio2 level during dendritogenesis (Fiore et al., 2009). These observations suggest miRNAs function as homeostasis keepers. Moreover, miRNA is also being accurately regulated in many circuits that guarantee the brain for normal function.

As we can conclude from the current status, experiments on brain miRNAs are scarcely systematic and apparently very primitive. One of the main obstacles of current miRNA research lies in the lack of panoramic view on the relationship among the large bunch of targeted genes by one single miRNA. High-throughput analysis of putative targets of miRNA can greatly accelerate the process to a thorough understanding of the biological functions of miRNAs. However, the partial complementary binding of miRNA to its targets and the variation in spatial distribution in different cell types make the bioinformatic prediction less credible. With recent advances in miRNA assay (Bell and Lewitter, 2009) and bioinformatics (Barbato et al., 2009; Spence, 2009; Ziegelbauer et al., 2009), at least part of the perplexing phenomenon, e.g. unmatched transcriptional and translational level, are expected to be solved. Although research data concerning the control of microRNAs on the development of specific brain regions and specific behaviors (such as learning, memory, mood, and addiction) are still lacking, it is hopeful that we will have a more clear recognition in the versatile role of miRNA in the regulation of neuronal development and brain function in the near future.

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