Cell. Mol. Life Sci. (2014) 71:3987–4005
DOI 10.1007/s00018-014-1671-7

Cellular and Molecular Life Sciences

REVIEW

MicroRNA-132, -134, and -138: a microRNA troika rules in neuronal dendrites

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Received: 5 March 2014 / Revised: 11 June 2014 / Accepted: 20 June 2014 / Published online: 10 July 2014

Abstract Dendritic mRNA transport and local translation in the postsynaptic compartment play an important role in synaptic plasticity, learning and memory. Local protein synthesis at the synapse has to be precisely orchestrated by a plethora of factors including RNA binding proteins as well as microRNAs, an extensive class of small non-coding RNAs. By binding to complementary sequences in target mRNAs, microRNAs fine-tune protein synthesis and thereby represent critical regulators of gene expression at the post-transcriptional level. Research over the last years identified an entire network of dendritic microRNAs that fulfills an essential role in synapse development and physiology. Recent studies provide evidence that these small regulatory molecules are highly regulated themselves, at the level of expression as well as function. The importance of microRNAs for correct function of the nervous system is reflected by an increasing number of studies linking dysregulation of microRNA pathways to neurological disorders. By focusing on three extensively studied examples (miR-132, miR-134, miR-138), this review will attempt to illustrate the complex regulatory roles of dendritic microRNAs at the synapse and their implications for pathological conditions.

Keywords miRNA · Neuron · Dendrite · Dendritic spine · Synaptic plasticity · Neurological disease

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Introduction

Mammalian neurons have a highly complex morphology with numerous branching dendrites and dendritic protrusions (i.e. spines) that serve to compartmentalize signals received from other cells. A single neuron can form thousands of synapses with other nerve cells, resulting in a coordinated network that underlies cognitive functions. The mechanisms by which the structure and composition of synapses change in response to neuronal activity are collectively referred to as "synaptic plasticity", and form the molecular foundation for information storage in the brain. Complex regulatory mechanisms are crucial for the physiological function of the nervous system.

Dendritic targeting of specific mRNAs allows for the dynamic regulation of the proteome via local translation at the synapse and is therefore an important determinant for synapse formation and activity-dependent synaptic plasticity (as reviewed by Holt and Schuman [1]). While only a handful of dendritically enriched mRNAs were initially reported, recent findings indicate that RNA localization to dendrites is a widespread phenomenon. For instance, microarray profiling of RNA preparations from compartmentalized hippocampal neuron cultures and from stratum radiatum led to the detection of about 100–200 transcripts localized in neuronal processes [2, 3]. Interestingly, recent deep sequencing analysis of the synaptic neuropil in the hippocampus identified 2,550 mRNAs present in dendrites and/or axons [4]. This enormous population of differentially localized transcripts highlights the importance of selective dendritic mRNA transport for subcellular protein sorting and implies an essential role of local translation in synapse morphology and function. Notably, local protein synthesis was visualized in isolated dendrites of hippocampal neurons [5] and linked to hippocampal synaptic plasticity [6, 7].

The mRNAs that are destined for dendritic transport are assembled into large ribonucleoprotein complexes (RNPs). These RNPs mediate both targeting and translational repression of mRNAs to ensure compartmentalized gene expression (as reviewed by Martin and Ephrussi [8]). Dendritic RNPs contain RNA binding proteins such as Fragile-X mental retardation protein (FMRP) as well as non-coding RNAs such as microRNAs (miRNAs) that mediate inhibition of protein synthesis. The specific composition of distinct RNA granules, such as transport RNPs, stress granules or processing bodies (P-bodies), is widely unknown and awaits to be addressed in future studies. For example, it is still unclear whether miRNA-mediated translational repression indeed occurs in P-bodies (as reviewed by Kiebler and Bassell [9]) or in a distinct class of RNPs [10]. Thus, an improved classification of neuronal granules will provide important information on RNA transport and metabolism.

Biogenesis, function and regulation of miRNAs

Over the last 20 years, miRNAs have emerged as an important class of small [$\sim$22 nucleotides (nt) long] non-coding regulatory RNAs with versatile functions in all aspects of development and physiology (as reviewed by Bushati and Cohen [11]). Biogenesis of miRNAs is a multistep process involving two RNase-dependent cleavage steps. The long primary miRNA transcript (pri-miRNA) is first cleaved in the nucleus by Drosha into the precursor miRNA (pre-miRNA), followed by Dicer processing in the cytoplasm. Finally, the mature miRNA is loaded into a multiprotein effector complex termed "miRNA-containing RNA induced silencing complex" (miRISC). Base pairing of the miRNA to complementary sequences within the 3′ untranslated region (3′ UTR) of target mRNAs results in translational inhibition and/or mRNA cleavage, thereby fine-tuning protein synthesis. Perfect binding of the so-called "seed" region (nt 2–7/8) at the 5′ end of the miRNA is the primary determinant for target specificity. As mismatches outside the seed can be tolerated, one miRNA is able to bind several different mRNAs. Furthermore, mRNAs can harbor numerous distinct miRNA binding sites, thereby considerably expanding the complexity of the miRNA regulatory network. Several excellent reviews provide a more comprehensive description of miRNA biogenesis and modes of action [12–17].

Due to their critical function as modulators of gene expression, miRNAs have to be precisely controlled in a spatiotemporal manner, and aberrant miRNA levels are often associated with disease. It is emerging that miRNAs are dynamically regulated at all stages of biogenesis and activity (as reviewed by Krol et al.; Siomi and Siomi; Trabucchi et al.; Newman and Hammond [18–21]). For example, there is evidence that regulation of miRNAs occurs at the level of transcription [22–24], pri-miRNA processing [25, 26], pre-miRNA processing [27–30], miRISC remodeling [31–33], and miRNA decay [34–37]. Notably, miRNAs have been reported to display a higher turnover rate in neuronal cells compared to non-neuronal cells. Interestingly, stimulation with glutamate was found to accelerate the miRNA turnover rate while blocking glutamate or preventing action potentials had the opposite effect, indicating that miRNA turnover is strongly affected by neuronal activity [34]. The accurate control of miRNA expression and activity might thus represent an important mechanism for neurons to dynamically adapt to changes, for example in the context of synaptic plasticity.

Role of miRNAs in the nervous system

Expression profiling and deep-sequencing studies indicate that hundreds of miRNAs are expressed in the brain at all developmental stages [38–42]. Moreover, using microarray analysis it was recently demonstrated that many miRNAs display development- and activity-dependent expression in primary hippocampal neuron cultures [43].

The functional relevance of the miRNA pathway in neuronal development was demonstrated for the first time in zebrafish, where Dicer deficiency caused severe defects in brain morphogenesis [44]. Furthermore, several studies in mice show that Dicer ablation in various brain regions impairs neuronal development and survival [45–47]. Moreover, Dicer deficiency in young adult mouse forebrain, controlled by the calcium/calmodulin-dependent kinase II α (CamK2α) promoter, results in shrinkage of cortical neurons and aberrant hyperphosphorylation of tau (a key feature of Alzheimer's disease) accompanied by neurodegeneration [48]. Interestingly, Dicer deletion induced in the forebrain of 8–10 weeks old mice leads to enhanced learning and memory [49], suggesting that the miRNA pathway is involved in the regulation of higher cognitive functions. These seemingly opposing effects following Dicer deletion could be explained by distinct subsets of miRNAs that are crucial during various developmental stages. Indeed, during early development miRNAs primarily promote neuronal differentiation, whereas at later stages miRNAs predominantly serve as molecular brakes during synaptic development and plasticity. In line with these findings, several individual miRNAs have been shown to play an important role in different aspects of plasticity in post-mitotic neurons.

In conclusion, miRNAs represent a vast regulatory network in the brain for dynamic control of neuronal differentiation, maturation, and function (as reviewed by Schratt; Fiore et al.; McNeill and Van Vactor [50–52]). Thus, it comes as no surprise that impaired miRNA

function has been implicated in a wide range of neurodevelopmental, neurodegenerative and neuropsychiatric diseases (as summarized in Table 1 and reviewed by Im and Kenny [53]).

Dendritic miRNA population

Several elegant studies used screening approaches to systematically identify miRNAs from the synaptodendritic compartment. First, laser capture dissection was performed to isolate somata and neurites from rat hippocampal neurons followed by multiplex real-time RT-PCR, which led to the identification of a set of miRNAs that were differentially expressed in cell bodies compared to neuronal processes [54]. Next, two independent screens analyzing synaptosome preparations from mouse and rat discovered an enrichment of several miRNAs in the synaptodendritic compartment by microarray technology [55, 56]. In addition, a screen for FMRP-associated miRNAs in mouse brain revealed a subpopulation of miRNAs including miR-125b and miR-132 as interactors of FMRP [57]. Taken together, these studies uncovered a whole network of dendritic miRNAs that could potentially fine-tune the local expression of crucial synaptic proteins and provide interesting candidates for future investigations. For example, the *N*-methyl-D-aspartate (NMDA) receptor 2A (GluN2A) transcript was found to be regulated by miR-125b [57] and post-synaptic density 95 (PSD-95) mRNA was identified as direct target of miR-125a [33]. Importantly, several reports demonstrated dendritic localization of key RISC components such as glycine–tryptophan repeat-containing protein of 182 kDa (GW182; also known as TNRC6A-C), Argonaute (AGO) proteins, as well as the DEAD box helicases DDX6 (also known as RCK or p54) and Moloney leukemia virus 10 (MOV10) [32, 58–60], pointing to a local activity of miRNAs in dendrites. Furthermore, several pre-miRNAs as well as the processing enzyme Dicer were found to be present in the synaptodendritic compartment [30, 55], suggesting a contribution of local pre-miRNA processing to dendritic miRNA expression. Moreover, polyribosomes as well as components and regulators of the translational machinery were detected in dendrites [61, 62]. These findings indicate a widespread role of the miRNA pathway in regulating local translation in dendrites.

Due to this complexity, this review focuses on three of the most extensively studied dendritic miRNAs with a well-documented function at the synapse—miR-132, miR-134 and miR-138. By describing these miRNAs in detail, we hope to illustrate the diversity of regulatory mechanisms governing activity-dependent transcription, miRNA processing and miRNA-mediated gene silencing in neurons. In addition, we will give examples of feedback loops and converging pathways of these three dendritic miRNAs. Thereby, we aim to delineate not only the function of individual miRNAs but also the crosstalks within the neuronal miRNA network, illustrating that miRNAs are a central hub for the fine-tuning of local protein synthesis involved in synaptic plasticity and neurological diseases.

Function of individual dendritic miRNAs

miR-134

miR-134 negatively regulates dendritic spine size

miR-134 is the first dendritic miRNA identified, for which a crucial synaptic function has been explicitly described. In the mouse genome, miR-134 is encoded as part of the miR-379–410 cluster, which encompasses 39 miRNAs. The miR-379–410 cluster is located within the paternally imprinted DLK1-GTL2 locus in mouse (DLK1-DIO3 region in human) and is conserved in mammals. Fluorescent in situ hybridization (FISH) analysis on primary hippocampal neurons from rat revealed that miR-134 localizes to dendrites, where it affects dendritic spine morphology [63]. Dendritic spines are small, actin-based membranous protrusions from the dendritic shaft and represent the postsynaptic part of most excitatory synapses. Importantly, the size of dendritic spines is strongly correlated with synaptic strength. Overexpression of miR-134 in hippocampal neurons led to a reduction in dendritic spine size, mediated by binding of miR-134 to complementary sequences in the LIM domain kinase 1 (Limk1) mRNA [63]. LIMK1 phosphorylates and thereby inactivates the actin depolymerizing factor cofilin, resulting in reorganization of the actin cytoskeleton [64, 65]. Interestingly, LIMK1 knockout mice display enhanced long-term potentiation (LTP) in the hippocampus and abnormalities in dendritic spine morphology [66] that are similar to the spine phenotype observed upon miR-134 overexpression in hippocampal neuron cultures [63]. Furthermore, inhibition of miR-134 activity with a 2′-*O*-methylated antisense oligonucleotide had the opposite effect and led to increased spine size [63]. Notably, miR-134-mediated inhibition of protein synthesis seems to be reversible, as the miR-134-dependent repression of Limk1 was relieved upon application of brain-derived neurotrophic factor (BDNF), a neurotrophin released by synaptic stimulation. It is possible that the relief of miRNA-mediated repression results from activity-induced post-translational modifications of RISC components, though this remains to be clarified in future studies. In conclusion, due to its dendritic localization and the reversibility of miR-134-mediated translational repression upon activation, miR-134 is well suited for regulating local translation in a precise spatiotemporal

Table 1 Altered levels of the "microRNA troika" in neurological disorders

MicroRNA	Disorder	Regulation, source/relevance	Potential target(s)	References
miR-132	Alzheimer's disease (AD)	↓, Human AD hippocampus, cerebellum and medial frontal gyrus	SIRT1, AChE, PTEN, FOXO3a and p300	[48, 109–112, 148]
		↓, Expression profiles from sporadic progressive supranuclear palsy (PSP) patients	PTBP2	
		↓, Postmortem human brain (superior and medial-temporal neocortex)		
		↓, Human hippocampus tissue of late onset AD (LOAD) patients	FOXO1a	
	Autism spectrum disorder (ASD)	↓, Human postmortem brain of ASD patients		[149–151]
		↓, Lymphoblastoid cell lines derived from ASD patients		
		↑, Peripheral blood mononuclear cells (PBMC) from ASD patients	MeCP2, PTEN, FMR1, HTR3a	
	Drug addiction	↑, Rat dorsal striatum after cocaine self-administration		[152]
	Epilepsy	↑, Mouse hippocampus, inhibition of miR-132 by LNA protects mouse CA3 against status epilepticus	Arg2	[115]
	Fragile X syndrome	↑, Mouse brain, associated with FMRP, overexpression of miR-132 in hippocampus neurons increased dendritic protrusion width and mEPSC amplitude	p250GAP	[57]
	Huntington disease (HD)	↓, Human HD cortex	p250GAP	[113, 114, 153]
		↓, Striata of two HD transgenic mice models		
		↑, Postmortem human brain (Brodmann's area 4)	MeCP2	
	Major depressive disorder (MDD)	↑, Serum samples from patients with depression		[154]
	Parkinson's disease (PD)	↓, Brain stem tissue from alpha-synuclein (A30P)-transgenic mice	SNX12, E2	[105, 106]
		↑, Mesencephalon brain areas of Berlin-Druckrey IV rats at P25	Nurr1	
	Rett syndrome (RTT)	↓, Rat cultured neurons	MeCP2	[92, 120]
		↓, Mecp2-null mouse cerebellum at P42	MeCP2	
	Schizophrenia (SZ)	↓, Postmortem human brain (dorsolateral prefrontal cortex, Brodmann's area 46)	DNMT3A, GATA2, DPYSL3	[122, 124]
		↑, Postmortem human brain (dorsolateral prefrontal cortex, Brodmann's area 46)	TH, PGD	
miR-134	Bipolar disorder (BD)	↓, Plasma level of drug-free, 2 week and 4 week medicated manic patients		[81]
	Epilepsy	↑, Mouse hippocampus, inhibition of miR-134 by LNA reduces status epilepticus and neuronal death	LimK1	[76]
	Schizophrenia (SZ)	↓, PFC and hippocampus, mouse model with 22q11.2 hemizygous deletion		[78–80]
		↓, Human PBMC		
		↑, Postmortem human brain (dorsolateral prefrontal cortex, Brodmann's area 46)		
miR-138	Alzheimer's disease (AD)	↑, Human cerebrospinal fluid of AD patients		[109, 111]
		↓, Human hippocampus tissue of late onset AD (LOAD) patients		
	Drug addiction	↑, D2 receptor-expressing cells of mouse striatum after cocaine treatment		[155]
	Epilepsy	↓, Brain tissue of temporal epilepsy patients with hippocampal sclerosis	SLC17A7	[141]
	Huntington disease (HD)	↓, Striata of two HD transgenic mice models		[113]
	Schizophrenia (SZ)	↑, Postmortem human brain (superior temporal gyrus, Brodmann's area 22)		[156]

Table 1 continued

MicroRNA	Disorder	Regulation, source/relevance	Potential target(s)	References
miR-212	Alzheimer's disease (AD)	↓, Superior and middle temporal cerebral cortex of AD patients		[157]
	Drug addiction	↑, Rat dorsal striatum after cocaine self-administration	SPRED1, MeCP2	[152, 158]
	Parkinson's disease (PD)	↓, Brain stem tissue from alpha-synuclein (A30P)-transgenic mice		[105]
	Rett syndrome (RTT)	↓, Mecp2-null mouse cerebellum at P42	MeCP2	[120, 123]
		↓, Postmortem human brain (dorsolateral prefrontal cortex, Brodmann's area 9)		
	Schizophrenia (SZ)	↓, PFC and hippocampus, mouse model with 22q11.2 hemizygous deletion		[78, 122]
		↑, Postmortem human brain (dorsolateral prefrontal cortex, Brodmann's area 46)	TH, PGD	

↑, Upregulated; ↓, downregulated

manner. Recently, miR-134 was found to be upregulated by NMDA and bicuculline treatment, indicating a potential role of this miRNA in other specific forms of plasticity, such as NMDA receptor-dependent long-term depression (LTD) and homeostatic synaptic plasticity [43].

Targeting of pre-miR-134 to dendrites

In addition to mature miRNAs, several pre-miRNAs have been identified in synaptosome purifications by real-time qRT-PCR [30, 55]. Detection of pre-miR-134 in synaptosomes was especially interesting due to the reported importance of mature miR-134 for dendritic spine development and synaptic plasticity [63, 67]. Dendritic accumulation of pre-miR-134 was verified by FISH on primary hippocampal neurons [30]. Furthermore, DHX36 (also known as RHAU, G4R1, or MLEL1), an RNA helicase of the DEAH-box protein family, was identified as a novel pre-miR-134 interacting protein in RNA pulldowns. DHX36 mediates dendritic localization of pre-miR-134 through specific binding to the loop region of pre-miR-134. Moreover, DHX36 binding to pre-miR-134 interfered with in vitro Dicer processing, indicating that DHX36 might serve to protect pre-miR-134 from premature cleaving during transport [30]. Notably, DHX36 was previously identified as an AGO2-associated protein in complexes devoid of Dicer [68, 69], supporting an additional role of DHX36 in the miRNA pathway downstream of pre-miRNA cleavage. Knockdown of DHX36 not only reduced dendritic pre-miR-134 accumulation, but also enhanced expression of miR-134 target reporter genes and increased dendritic spine size [30], most likely due to decreased dendritic miR-134 activity. This discovery shed light on the long-standing question of how miRNAs are selectively transported to dendrites, a prerequisite for a functional role of miRNAs at synapses. We hypothesize that dendritic pre-miR-134 offers a source for local expression of miR-134 in dendrites, for example by local Dicer processing in response to synaptic stimulation, though this awaits to be addressed in future studies.

Interestingly, mature miR-134 is able to independently translocate to dendrites upon microinjection [63], demonstrating that dendritic transport also occurs at the level of the mature miRNA. It is tempting to speculate that these two dendritic targeting mechanisms for miR-134 are not mutually exclusive, but rather work in parallel, regulating two different miR-134 pools in neurons. On the one hand, the bulk of dendritic miR-134, which likely originates from processing at the cell body, might serve to mediate translational repression of miR-134 target mRNAs during transport along dendrites to prevent premature expression of plasticity-related proteins. On the other hand, miR-134 derived from dendritic pre-miR-134 might represent a reserve pool which allows rapid increases in miR-134 levels at individual synapses upon activation. This could be important for synaptic tagging (as reviewed by Martin and Kosik [70]) or local forms of homeostatic plasticity [71]. Further studies are required to clarify if other dendritic miRNAs depend on similar or distinct transport mechanisms to reach their final destination at the synapse.

Activity-dependent transcription of miR-134 regulates dendritogenesis

Numerous miRNAs including miR-134 display a tissue- or developmental stage-specific expression pattern, which is partially attributed to transcriptional regulation. Transcription of miRNAs from the miR-379–410 cluster, among them miR-134, was found to be induced upon neuronal activation in a co-regulatory manner. Application of KCl or BDNF resulted in a transient induction of miR-134 expression, mediated by binding of the transcription

factor myocyte enhancing factor 2 (MEF2) to a regulatory element located ~15 kb upstream of the cluster [22]. Importantly, induction of miR-134 as well as other miRNAs from the miR-379–410 cluster (miR-381 and miR-329) is required for activity-dependent dendritogenesis in primary hippocampal neurons. The effects of miR-134 on dendritogenesis are mediated by repression of the miR-134 target Pumilio 2 (PUM2), an RNA-binding protein involved in RNA transport, which exerts mainly repressive effects on translation [22]. Moreover, recombinant adeno-associated virus (rAAV)-mediated overexpression of miR-134 in cortical layer V pyramidal neurons resulted in impaired dendritic arborization in vivo [72]. Interestingly, both miR-134 inhibition in primary hippocampal neurons [22] and miR-134 overexpression in vivo [72] result in the same phenotype of reduced dendritic outgrowth. These findings suggest that miR-134-mediated fine-tuning of PUM2 protein levels is crucial for dendritogenesis.

Implication of miR-134 for synaptic plasticity and memory

The first evidence for a crucial role of miR-134 in learning and memory came from the discovery that miR-134 expression is controlled by the histone deacetylase sirtuin1 (SIRT1) [67]. SIRT1 mediates transcriptional repression via interaction with a complex containing the sequence-specific transcription factor Yin Yang 1 (YY1), which binds ~5 kb upstream of the miR-134 gene. SIRT1Δ mice lacking SIRT1 catalytic activity specifically in the brain displayed impaired synaptic plasticity and abrogated long-term memory formation during fear conditioning [67]. SIRT1 deficiency was accompanied by transcriptional upregulation of miR-134 and a concomitant translational repression of cAMP responsive binding protein (CREB), a key plasticity gene and newly identified miR-134 target. Downregulation of CREB in turn resulted in reduced expression of BDNF, consistent with the observed impairment of synaptic plasticity. Interestingly, lentivirus-mediated overexpression of miR-134 in the CA1 area of the hippocampus in a wildtype background led to aberrant LTP and impaired hippocampus-dependent memory formation during fear conditioning, thereby mimicking the deficiencies observed in SIRT1Δ mice. Moreover, inhibition of miR-134 upon hippocampal injection of a locked nucleic acid (LNA)-based antisense oligonucleotide restored CREB and BDNF levels and rescued the plasticity and memory impairments in SIRT1Δ mice [67].

Recently, the described SIRT1 phenotypes have been recapitulated using a pharmacological approach [73]. On the molecular level, resveratrol reduced miR-134 and miR-124 levels and increased the expression of both CREB and BDNF. Importantly, resveratrol and SIRT1 have been reported to exert neuroprotective effects in models for Alzheimer's disease [74]. Thus, the SIRT1/miR-134 pathway represents a potential therapeutic target in the context of neurodegeneration and memory impairments.

Role of miR-134 in neurological disorders

Epilepsy is a neurological disorder characterized by recurring seizures that result from abnormal neuronal firing. Despite intense research, the molecular mechanisms underlying epileptic seizures are still widely unknown, but there are indications that miRNAs could play an important role in epileptogenesis (as reviewed by Henshall [75]). Recently, changes in miR-134 levels have been connected to epilepsy. Prolonged seizures evoked by intra-amygdalar injections of kainic acid in mice were reported to upregulate miR-134 expression [76]. In addition, RISC loading of miR-134 was enhanced upon status epilepticus, accompanied by decreased protein levels of the miR-134 target LIMK1. Importantly, knockdown of miR-134 by injection of LNA-based, cholesterol-modified antisense oligonucleotides prior to seizure induction decreased seizure severity during status epilepticus and reduced neuronal cell death. Moreover, also inhibition of miR-134 after status epilepticus had an anti-epileptic effect. Notably, increased miR-134 levels and concomitant reduced levels of LIMK1 were also detected in temporal lobe epilepsy patients [76]. In line with these findings, upregulation of miR-134 was also reported in a pilocarpine rat model of status epilepticus and in children with mesial temporal lobe epilepsy [77]. Together, these studies demonstrate a critical role for miR-134 in epilepsy. Importantly, neurological diseases are often accompanied by aberrant changes in dendritic spine morphology. Jimenez-Mateos et al. [76] reported unexpected morphological alterations in the context of epilepsy, where inhibition of miR-134 in vivo significantly reduced the dendritic spine density of hippocampal CA3 pyramidal neurons. Notably, this observation is in contrast to previous results from cultured hippocampal neurons reporting an increase in spine volume, but no changes in spine density upon miR-134 inhibition [63]. Further investigations are needed to clarify if these conflicting results are due to different subcellular localization of the inhibitors (cell body versus dendrites) and/or effects of miR-134 targets other than LIMK1. Moreover, the analysis of miR-134 knockout mice will help to elucidate if these opposing findings result from differences between in vitro and in vivo conditions.

Interestingly, in a mouse model of schizophrenia (SZ), altered miRNA expression levels including a downregulation of miR-134 in the prefrontal cortex and the hippocampus and a concomitant reduced dendritic spine density were observed and linked to defects in the miRNA biogenesis pathway [78]. On the contrary, a miRNA

profiling study on postmortem human brain tissue (dorsolateral prefrontal cortex Brodmann area 46) from SZ patients reported an upregulation of Dicer and several miRNAs including miR-134 [79]. These discrepancies likely reflect the different organisms, tissues, and developmental stages analyzed and suggest that deducing a function for specific miRNAs based solely on changes in expression profiles is challenging. Additional studies will be needed to clarify whether aberrant miRNA expression profiles reflect the cause or rather the consequence of certain pathological conditions.

A recent expression profiling study investigating the association of altered miRNA expression with SZ in humans revealed downregulation of several miRNAs from the DLK1-DIO3 region (located on human chromosome 14) including miR-134 in peripheral blood mononuclear cells of SZ patients [80]. Furthermore, profiling of blood miRNA levels in bipolar disorder (BD) patients reported a correlation between decreased miR-134 plasma levels and bipolar mania [81]. These studies indicate that miRNAs in biofluids, in particular miR-134, might represent valuable biomarkers for monitoring neurological disease progress and therapeutic response, although this clearly still requires further investigations.

In conclusion, miR-134 allows precise fine-tuning of local protein synthesis at the synapse due to the complex regulation of its own expression at the transcriptional and post-transcriptional level. Thereby, miR-134 contributes to dendritic spine remodeling, an important mechanism underlying learning and memory. Since impairments in dendritic spine morphology are a hallmark in the pathogenesis of several neurological diseases, miR-134 represents a promising novel target for therapeutic intervention.

miR-132

Genomic organization and transcriptional regulation of the miR-212/132 cluster

The miR-212/132 family is highly conserved in vertebrates and was discovered almost 10 years ago (as reviewed by Tognini and Pizzorusso [82], Wanet et al. [83]). Both miR-132 and miR-212 derive from the same primary transcript (chromosome 17p13.3 in humans), and might share the same mRNA targets due to their identical seed region. While miR-132 and miR-212 are both expressed in brain and testes, miR-212 is in addition expressed in the heart and mammary glands [84]. Albeit being expressed from the same transcript, expression levels of mature forms of miR-132 and miR-212 are largely different, most likely due to post-transcriptional regulatory mechanisms.

In neuronal cells the miR-212/132 locus was identified as a target of CREB which binds to at least four conserved sites present in the mouse miR-212/132 promoter, suggesting that CREB is a central regulator of activity-dependent miR-212/132 expression [23, 85]. Furthermore, it was demonstrated by Wibrand et al. [86] that the expression levels of the primary and precursor forms of miR-212 and miR-132 were induced in parallel during LTP in the rat adult dentate gyrus. Subsequently, using small RNA sequencing, Remenyi et al. [85] found that miR-132 and miR-212 were the most upregulated miRNAs upon BDNF stimulation of primary cortical mouse neurons. They found that the transcription of the miR-212/132 cluster is regulated by the extracellular signal regulated-kinase 1/2 (ERK1/2) pathway, acting upstream of mitogen and stress-activated kinase 1 (MSK1) and the phosphorylation of CREB. Intriguingly, in several studies stimulus-dependent upregulation was observed specifically for miR-132, but not for miR-212, possibly as a result of increased stability of mature miR-132 and/or preferential processing of pre-miR-132. Therefore, further studies are required to elucidate the underlying molecular mechanisms by addressing the differential regulation of these two miRNAs. For the remainder of this chapter, we will focus mainly on miR-132, since this miRNA has been implicated in several processes of synaptic development and function by multiple studies [57, 87–90].

Role of miR-132 in neuronal morphogenesis

miR-132 induces neurite outgrowth and modulates dendrite morphology of cortical and hippocampal neurons by repressing the expression of the GTPase-activating protein p250GAP [23, 24]. Impey et al. [91] showed that miR-132-mediated inhibition of p250GAP activates the RAC1-PAK actin-remodeling pathway and thereby regulates activity-dependent spine plasticity in hippocampal neurons. In addition, miR-132 was reported to target methyl CpG-binding protein 2 (MeCP2) [92], a known regulator of neuronal maturation, synapse formation as well as dendrite and axon branching [93, 94]. Therefore, it is tempting to speculate that miR-132 might regulate neurite extension also by fine-tuning MeCP2 levels, albeit a direct link has to be provided by future studies. In addition, it was proposed that MeCP2 regulates BDNF, which itself triggers the induction of miR-212/132 expression. This suggests a feedback mechanism whereby miR-132 is a central regulator of the homeostatic control of MeCP2 expression [92]. Kawashima et al. [95] further demonstrated that miR-132 overexpression increases expression of the glutamate receptors GluA1, GluN2A and GluN2B in cultured rat cortical neurons, while miR-132 inhibition prevents the BDNF-dependent upregulation of these proteins, suggesting that the function of miR-132 in these BDNF-dependent processes might be indirect. The central role of miR-132 in

neuronal morphogenesis was further confirmed in several in vivo studies. Magill et al. [87] reported decreased spine density, spine length and arborization of newborn neurons in the mouse adult hippocampus upon deletion of the miR-212/132 locus, thereby providing support for a positive role of miR-132 in neuronal morphogenesis in vivo.

Role of miR-132 in neuronal plasticity and synapse formation

Nudelman et al. [96] demonstrated an upregulation of pri-miR-212/132 by different activity paradigms in juvenile mice, indicating that miR-132 expression might play a fundamental role in activity-dependent synaptic plasticity in the intact animal. Accordingly, sponge-based sequestration of miR-132 led to reduction in synapse formation and an impairment of the functional integration of newborn neurons in the olfactory bulb [97]. In addition, two studies show that miR-132 is a key regulator of ocular dominance plasticity [98, 99]. In both studies, visual stimulation was reported to upregulate miR-132 in the visual cortex. Tognini et al. [99] demonstrated that light exposure enhanced positive epigenetic marks within the miR-212/132 promoter resulting in increased transcription of the miR-212/132 locus. Consistent with a positive role of miR-132 in neuronal maturation, upregulation of miR-132 led to an increase in mature dendritic spines, while downregulation of miR-132 caused more immature spines and disrupted ocular dominance plasticity [98]. Together, these studies demonstrate the critical contribution of experience-dependent miR-132 expression to developmental plasticity in mammals.

Importantly, miR-132 function is not limited to the regulation of structural and functional plasticity, but also impinges on higher cognition. Hansen et al. [100] showed that fivefold overexpression of miR-132 in transgenic mice resulted in increased spine density and deficits in novel object recognition memory. In a follow-up study that explored the function of miR-132 under more physiological conditions, Hansen et al. [89] carefully titrated miR-132 expression levels using a doxycycline-regulated miR-132 transgenic mouse strain. Indeed, subtle over-expression of miR-132 in the hippocampus enhanced cognitive capacity, which is more consistent with its previously reported positive function in neuroplasticity. Overall, these findings suggest that miR-132 expression levels are tightly regulated within a narrow range to ensure normal learning and memory formation. In the future, a transgenic mouse model in which miR-132 is placed downstream of an activity-regulated promoter would represent a valuable tool to study the activity-dependent component of miR-132 in neuronal development and plasticity. Similar models have been generated in the past for other highly activity-dependent genes such as BDNF [101].

miR-132 dysfunctions and diseases in the brain

Given the versatile roles of miR-132 in neuronal connectivity and synaptic plasticity, it is not surprising that altered expression patterns of this activity-regulated miRNA are associated with a series of neurological disorders (as summarized in Table 1 and reviewed by Im and Kenny [53], Goodall et al. [102], Eacker et al. [103]).

Parkinson's disease (PD) is characterized by progressive neurodegeneration of dopaminergic neurons in the substantia nigra. Conditional knockout of Dicer in dopaminergic mouse neurons results in a progressive loss of these cells, suggesting that miRNAs are critical for the homeostasis of the dopaminergic system [104]. Concerning miR-132 and miR-212 specifically, reduced expression of these miRNAs was found in the brain of α-synuclein (A30P)-transgenic mice, a well-established PD model [105]. In contrast, Lungu et al. [106] demonstrated a significant upregulation of miR-132 in mesencephalic brain areas of another PD rat model (Berlin-Druckrey IV affected) by microarray and qRT-PCR. Furthermore, expression of the known miR-132 target nuclear receptor related 1 protein (NURR1), which is involved in the neurogenesis of midbrain dopaminergic neurons, was inversely correlated with miR-132 levels [107].

Emerging evidence furthermore implicates impaired miR-132 expression in Alzheimer's disease (AD; as reviewed by Tan et al. [108]). Lau et al. [109] reported a downregulation of miR-132 in the human hippocampus and prefrontal cortex of AD patients. Smith et al. [110] found miR-132 to be downregulated in patients suffering from progressive supranuclear palsy, another tauopathy. They suggest that miR-132 is involved in this disorder by targeting the neuronal splicing factor polypyrimidine tract binding protein 2 (PTBP2) [110]. A downregulation of miR-132 in AD patients has been further confirmed in other studies investigating different brain tissues (hippocampus, cortex) [111, 112]. In further support of an involvement of miR-132 in AD, several genes that are upregulated in AD, including Phosphatase and Tensin Homolog (PTEN), E1A binding protein p300 (P300), Forkhead box O1a (FOXO1a) and Forkhead box O3a (FOXO3a) are known miR-132 targets [109, 112].

miR-132 is likely involved in another prominent neurodegenerative disorder, Huntington's disease (HD). Interestingly, downregulation of miR-132 expression was demonstrated in two HD mouse models and in the brain of human HD patients [113, 114]. Mechanistically, miR-132 downregulation in the human HD cortex appears to result from increased expression of the inhibitory transcription factor RE1-silencing transcription factor (REST), which is known to silence neuronal gene expression in non-neuronal cells under non-pathological conditions [114].

Similar to miR-134, miR-132 also appears to be involved in epilepsy. Jimenez-Mateos et al. [115] detected high expression of endogenous miR-132 in the mouse brain 24 h after seizure activity. Although inhibition of both miRNAs with antisense oligonucleotides shows a protective effect against seizure damage in the hippocampus CA3 region, only inhibition of miR-134, but not of miR-132 has apparent effects on seizure severity, suggesting that the downstream targets of these two miRNAs are largely non-overlapping [76, 115].

In addition to its participation in neurodegenerative disorders, miR-132 might also play an important role in neurodevelopmental diseases characterized by intellectual disability, such as Rett (RTT) and Fragile X syndrome (FXS) (as reviewed by Fineberg et al. [116], Siew et al. [117]). RTT is an X-linked neurodevelopmental disorder caused by loss-of-function mutations in the MeCP2 gene (as reviewed by Na and Monteggia [118]). Interestingly, MeCP2 gene duplications also result in RTT-like symptoms, suggesting that keeping MeCP2 levels near a given set point is critical for proper neuronal development (as reviewed by Samaco and Neul [119]). The already described connection of MeCP2 and miR-132 could therefore play a role in RTT aetiology. Using a genome-wide analysis of miRNA expression in a RTT mouse model, both miR-212 and miR-132 were shown to be downregulated in the cerebellum, accompanied by decreased BDNF levels [120]. It will therefore be interesting to test whether restoring miR-132/212 expression in RTT mice is sufficient to ameliorate the neuromorphological and behavioral defects. FXS on the other hand is caused by loss of FMRP and is the leading genetic cause for intellectual disability and autism. Several links between FMRP and the miRNA pathway have been reported, including an interaction of FMRP with Dicer, Ago1 and specific mature miRNAs [57, 121]. Intriguingly, one of the FMRP-interacting miRNAs is miR-132 and FMRP appears to be required for the spine regulatory function of miR-132 [57]. It is therefore tempting to speculate that the observed spine defects in FXS might be at least partially dependent on the loss of miR-132 function.

Finally, large-scale miRNA profiling studies also demonstrated altered miR-132 levels in neuropsychiatric disorders like SZ. Interestingly, aberrant miR-132 and miR-212 expression patterns were identified in the prefrontal cortex in patients affected with BD and SZ [122, 123]. Kim et al. [122] investigated the expression levels of miR-132 and miR-212 among others, in the prefrontal cortex of individuals with SZ and BD, and found that these miRNAs were significantly upregulated in SZ patients. In contrast to these findings, Miller et al. [124] found a downregulation of miR-132 in the prefrontal cortex of schizophrenic patients and a concomitant upregulation of validated miR-132 target genes, such as DNMT3A, GATA2 and DPYSL3. This is yet another example illustrating that miRNA profiles obtained from patients suffering from rather complex disorders are very heterogeneous and influenced by a number of parameters, including but not limited to the methods of miRNA isolation and profiling, and perhaps even more importantly, the tissue and developmental stage analyzed. Further confounding variables are the assignment to different disease categories and the composition of patient and control cohorts. More standardized procedures are therefore necessary to obtain more reliable data regarding alterations in miRNA expression from clinical samples.

Taken together, numerous studies demonstrate the importance of miR-132 biogenesis and regulation in normal brain development and function and also make miR-132 one of the prime candidates for follow-up studies in neurodevelopmental and neuropsychiatric disorders. Before miR-132 could be considered as potential novel therapeutic option in these diseases, a better mechanistic understanding of the miR-132 regulated pathways will be required.

miR-138

Local expression of miR-138 and its two precursor forms

miR-138 is another extensively studied neuronal microRNA with various functions in development, plasticity and disease. Two genomic loci (MIR138-1, MIR138-2) on different chromosomes encode for distinct precursor forms of miR-138. The two miR-138 genes have been initially identified in mice but also have conserved homologues in the human genome [125, 126]. Although eventually both hairpin structures can give rise to the same 23 nt long mature form of miR-138, the size of the precursors, the sequences surrounding the stem-loop as well as the transcription levels of the two primary miRNAs seem to largely differ. While in an initial study the shorter 62 nt form of pre-miR-138-1 could not be detected using Northern Blot, the 69 nt long pre-miR-138-2 was found to be highly and ubiquitously expressed among different tissues as well as developmental stages [27], suggesting that the mature miR-138 is mainly derived from the highly transcribed pri-miR-138-2. It is important to note that the expression of mature miR-138 does not mimic the ubiquitous expression of pre-miR-138-2, but is rather restricted to individual tissues and cell types, most notably the brain. This is especially interesting as it demonstrates a possible post-transcriptional regulation of mature miRNA expression, most likely at the level of Dicer processing, thereby providing an additional transcription-independent control mechanism for regulating miR-138 expression.

Within the brain miR-138 seems to be mostly expressed in cells of the neocortex, the hippocampus, as well as

granule and Purkinje cells of the cerebellum [27, 127]. On a subcellular level miR-138 belongs to the group of miRNAs found to be locally enriched at synaptic sites [56], which provided a rationale that it could be involved in local dendritic translation and synaptic mechanisms. Interestingly, not only mature miR-138, but also both of its precursors have been identified in synaptosome purifications, where pre-miR-138-2 shows a significant enrichment [30]. Analogous to the situation already described earlier for miR-134, pre-miR-138 could therefore provide a local source for the production of miR-138 at synapses, although experimental evidence for pre-miR-138 dendritic transport or processing is still lacking.

Role of miR-138 in the regulation of dendritic spine size

A function of miR-138 at the synapse has first been observed in primary rat hippocampal neurons, where it was shown to be important for restricting spine size. This was paralleled by a miR-138-dependent decrease in synaptic transmission as shown by a reduction in miniature excitatory postsynaptic currents (mEPSCs) upon miR-138 overexpression [56]. miR-138 effects were mediated by the direct targeting of the depalmitoylation enzyme acyl-protein-thioesterase 1 (APT1). More specifically, miR-138-dependent translational repression of APT1 leads to reduced depalmitoylation of the $G_{\alpha}13$ subunits of G proteins, which increases their membrane association. In their palmitoylated and thus membrane-bound state, $G_{\alpha}13$ subunits lead to the continued activation of the downstream RhoA pathway [128] which in turn induces actomyosin contraction and spine shrinkage [129]. The miR-138/Apt1 interaction was more recently confirmed in an additional study [32]. The authors detected colocalization of miR-138 and Apt1 mRNA in dendrites as well as local translational repression of Apt1 by miR-138. In addition, the study revealed an activity-dependent degradation of the RISC component MOV10 upon NMDA stimulation followed by local translation of known miRNA-targets, including Apt1. The ubiquitin-dependent proteasomal degradation of MOV10 seems to occur specifically at activated synapses, relieving RISC-dependent translational repression locally. This mechanism seems to be conserved in Drosophila, where the MOV10 homolog Armitage is involved in local translation of CaMKII and memory formation [31].

Additional functions of miR-138 in cell migration and axon regeneration

In addition to the well-described function of miR-138 in dendrites of mature neurons, more recent studies have uncovered additional roles and targets of this miRNA in other stages of neuronal development and function such as cell migration [130] and axon regeneration [131]. For example, ectopic overexpression of miR-138 was found to enhance hypothalamic cell migration. The extracellular matrix glycoprotein Reelin (RELN) was suggested as a direct miR-138 target based on luciferase reporter gene experiments and Ago2-immunoprecipitations [130]. The role of RELN secretion in neuronal migration in the developing brain and in the formation of cell–cell contacts has been extensively studied and covered by excellent reviews [132, 133]. In this context, it is especially noteworthy that impaired RELN expression has been implicated in a variety of neurological diseases, including SZ [134], BD [135] and AD [136], among others [137]. Since miR-138 levels are frequently changed in some of these disorders (Table 1), it is tempting to speculate that impaired miR-138-dependent RELN regulation could contribute to disease phenotypes, although no causal link has yet been established. However, since miRNAs are known to target hundreds of different mRNAs, a variety of other miR-138 targets and combinatorial effects are likely to be involved in the etiology of complex neurological disorders. In fact, SIRT1 has recently been identified as a third target of miR-138 with possible connections to neurodevelopment and disease [131]. SIRT1 is well known as a key regulator of metabolic, gene expression and genomic stability processes that are closely related to aging (as recently reviewed by Herskovits and Guarente [138]). Liu et al. [131] found that high miR-138 levels and a resulting repression of Sirt1 mRNA translation leads to an inhibition of axon growth in developing cortical neurons and negatively regulates axon regeneration of adult sensory neurons in vivo.

Interestingly, SIRT1 itself negatively regulates the transcription of other miRNAs including miR-134 (see chapter on miR-134 in this review; [67]), suggesting a crosstalk between different plasticity-regulating miRNAs at the level of SIRT1. miR-138 expression similarly appears to be dependent on SIRT1 levels, since mature miR-138 levels are affected by SIRT1 knockdown/overexpression. Using chromatin immunoprecipitation (ChIP), direct binding of SIRT1 to a regulatory region upstream of the pre-miR-138-1 gene was observed [131]. It should be noted however that this feedback loop involves pre-miR-138-1, but not pre-miR-138-2 which appears to be the predominant precursor for the generation of mature miR-138. Closer investigation of the interplay of both genes and their precursor forms will therefore be necessary to reveal the precise control mechanisms that underlie miR-138 expression.

Regulation of miR-138 expression by activity and the circadian clock

Given its role in regulating the growth of synapses and other activity-dependent neuronal processes it is not

surprising that miR-138 levels are regulated by neuronal activity. Chemical stimulation of primary hippocampal cultures with KCl leads to decreased levels of this miRNA [56] and a similar trend of downregulation was seen in the hippocampus of mice after neuronal activity has been simulated by electroconvulsive shock [139]. Additionally, the induction of NMDA-dependent chemical LTP and LTD in cultured neurons seem to have opposing effects on miR-138 levels in the way that LTP induces a reduction and LTD an increase in miR-138 levels [43]. The direction of these changes is consistent with the repressive function of miR-138 in spine growth. The mechanisms underlying activity-dependent decrease of miR-138 are so far unknown and could involve regulation at the level of transcription, processing of the precursors or stability of the mature form.

Furthermore, miR-138 levels may not only be determined by the activity status of the cell, but could also be regulated by a cell intrinsic circadian clock. A recent study suggests that miR-138 is among a group of miRNAs that are increased at a pre-light onset compared to a pre-dark onset [140]. In this study, increased miR-138 levels could be observed in several brain areas, including hippocampus, hypothalamus and prefrontal cortex, among others. Whether miR-138 is functionally involved in the establishment of circadian rhythms remains to be determined.

Role of miR-138 in brain dysfunctions

In line with activity-dependent regulation of miR-138 during synaptic plasticity and homeostasis, a recent study found reduced miR-138 levels in brain tissue of patients with mesial temporal lobe epilepsy, a pathological condition characterized by excessive neuron activation and seizures [141]. Interestingly, miR-138 levels were only reduced in patients with hippocampal sclerosis, but not in patients without this tissue damage. It is therefore tempting to speculate that a precise regulation of miR-138 and accordingly its targets is involved in cellular processes that protect neurons from disturbances in network activity. However, whether miR-138 alterations are the cause or just a consequence of these maladaptations during epileptogenesis is completely unclear.

Altered miR-138 levels were also found in malignant gliomas, a particularly aggressive form of brain tumors [142]. Serving as an oncogene, miR-138 is upregulated in the highly tumorigenic glioma stem cells (GSCs) where it promotes their growth and survival by altering the expression of so far unknown tumor suppressors. This study indicates that targeting miR-138 in the glial cell lineage could be a promising strategy to interfere with glioma formation and/or progression.

miR-138 regulation in other cell types

miR-138 has also been studied in other cell types and even though the role of these findings and their significance for neuronal cells is unknown, they might provide interesting insights into miR-138 biology in general. For example, a possible new regulatory mechanism of miR-138 activity has been recently identified in the form of circular RNA (circRNA) sponges [143]. In these circRNAs the 5′ and 3′ends of a single RNA molecule are connected due to a head-to-tail splicing event. The resulting circular structure confers high stability to the RNA molecule compared to linear counterparts. It has been known for quite some time that one of these circRNA is transcribed from the *SRY* (sex-determining region Y) gene and rather specifically expressed in testes [144]. It was now demonstrated that the *Sry* circRNA possesses 16 miR-138 binding sites and is thereby able to inhibit miR-138 function via a natural sponge-like mechanism [143]. Whereas circ*Sry* is highly testes-specific, several other circRNA have been shown to be expressed in the brain [145] and their possible sponge function might provide another mechanism involved in the regulation of miRNA activity.

The mutual regulation of SIRT1 and miR-138 already provided a link between miR-138 and other miRNAs, such as miR-134. However, the effect of miR-138 on other miRNAs could be even more global. In HeLa cells miR-138 expression seems to reduce the stability of Exportin5, a crucial factor for nuclear export of most precursor miRNAs, by targeting required for meiotic nuclear division 5 homolog A (RMND5A) [146]. It remains to be examined whether this regulatory interaction takes place in neurons and what might be the functional consequences in the context of neurodevelopment and plasticity.

In conclusion, accumulating evidence establishes miR-138 as an important player in a variety of neuronal mechanisms, ranging from neuronal differentiation and migration to axonal pathfinding and synaptic plasticity. miR-138-regulated pathways are therefore promising targets for intervention in diverse neurological disorders.

Interconnections of dendritic miRNAs

Individual neurons are embedded into complex and plastic neuronal networks. Maintaining a stable physiological state within these networks while being able to rapidly respond and adapt to activity-dependent changes, requires a sophisticated control over gene expression that has to be carefully timed and localized. An elaborate network of regulating factors is necessary for this process, which includes the miRNAs discussed in this review. It comes as no surprise that in such a complex system also these

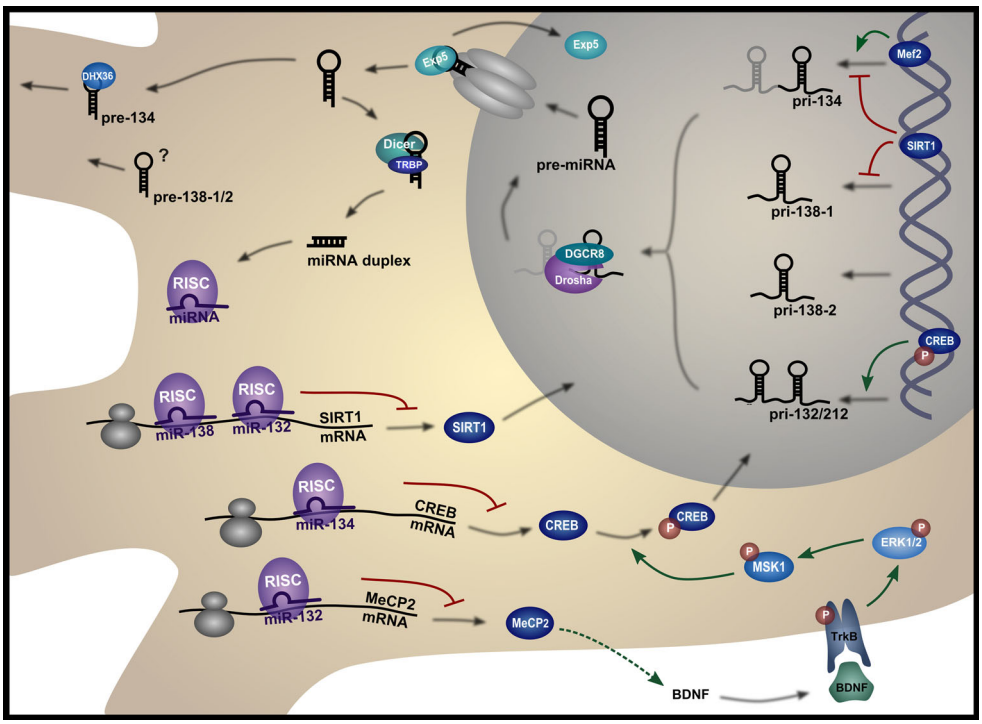

Fig. 1 Biogenesis and regulation pathways of dendritic miRNAs. The miRNA gene is transcribed into a primary miRNA transcript (pri-mRNA) which is cleaved by Drosha to generate a hairpin miRNA precursor (pre-miRNA). After nuclear export, the pre-miRNA is cleaved by Dicer to form the double-stranded miRNA duplex. One strand of this duplex, the mature miRNA, is then incorporated into the miRNA-induced silencing complex (miRISC). The miRISC complex can bind to complementary target mRNAs, thereby repressing their translation. This figure depicts those targets that are in turn regulating miRNA expression in neurons (see text for further details)

regulators themselves are subject to tight control mechanisms that are highly interconnected. Hence, a variety of feedback loops and interplays between the different miRNA pathways have been identified.

The mutual regulation of miR-138 and SIRT1 demonstrates a mechanism by which miRNAs can influence their own expression levels (Fig. 1). While SIRT1 is involved in the transcriptional control of one of the two miR-138 precursors, mature miR-138 regulates the translation of SIRT1 protein, thereby repressing its own repressor [131]. Notably, the pathways of several miRNAs converge on SIRT1 as its mRNA is targeted not only by miR-138, but also by miR-132 [147]. Further, SIRT1 in turn promotes the transcriptional repression of miR-134 [67], in addition to miR-138.

The transcription factor CREB represents another important crosstalk point of dendritic miRNA pathways (Fig. 1). First, CREB has been shown to induce expression of the miR-212/132 locus [23]. Furthermore, Creb mRNA itself is subject to miRNA-dependent translational repression and miR-134 was shown to be one of the miRNAs that targets Creb mRNA [67]. In addition, miR-132 itself is indirectly involved in CREB activation by targeting the mRNA of MeCP2, an important transcriptional regulator in neurons that also induces BDNF expression. BDNF in turn triggers signaling pathways leading to the activation of CREB as a transcriptional regulator [92]. This feedback loop might therefore provide a mechanism for homeostatic regulation of the implicated factors by fine-tuning their expression levels.

In addition to crosstalk at the level of miRNA expression, dendritic miRNAs can also merge on downstream pathways on the functional level. This becomes evident when focusing on the functional effects of miR-132, miR-134 and miR-138 on spine growth (Fig. 2). All three miRNAs target components that are involved in the formation and remodeling of the actin cytoskeleton [56, 57, 63], with both miR-132 and miR-134 influencing LIMK1 activity. While miR-134 inhibits LIMK1 expression by targeting its mRNA directly [63], miR-132 indirectly leads to activation of LIMK1 as it represses the mRNA of p250GAP, which in turn is a known repressor of the LIMK1 activating factor RAC [23]. This demonstrates how two miRNAs can have opposing effects on spine morphogenesis by targeting different components in the same signaling pathway.

Overall, the interconnections between the pathways of these miRNAs are a reflection of the huge complexity of activity-dependent processes in neurons and the tight regulation of underlying regulatory mechanisms. This is further highlighted by the fact that during the last years an increasing number of other miRNAs was found to be involved in morphological and functional changes of dendrites and dendritic spines. Although this review aims at giving a more detailed overview of the probably best-studied examples, miR-132, miR-134 and miR-138, Table 2 provides a comprehensive overview of additional miRNAs that have emerged as important regulators of dendritic function.

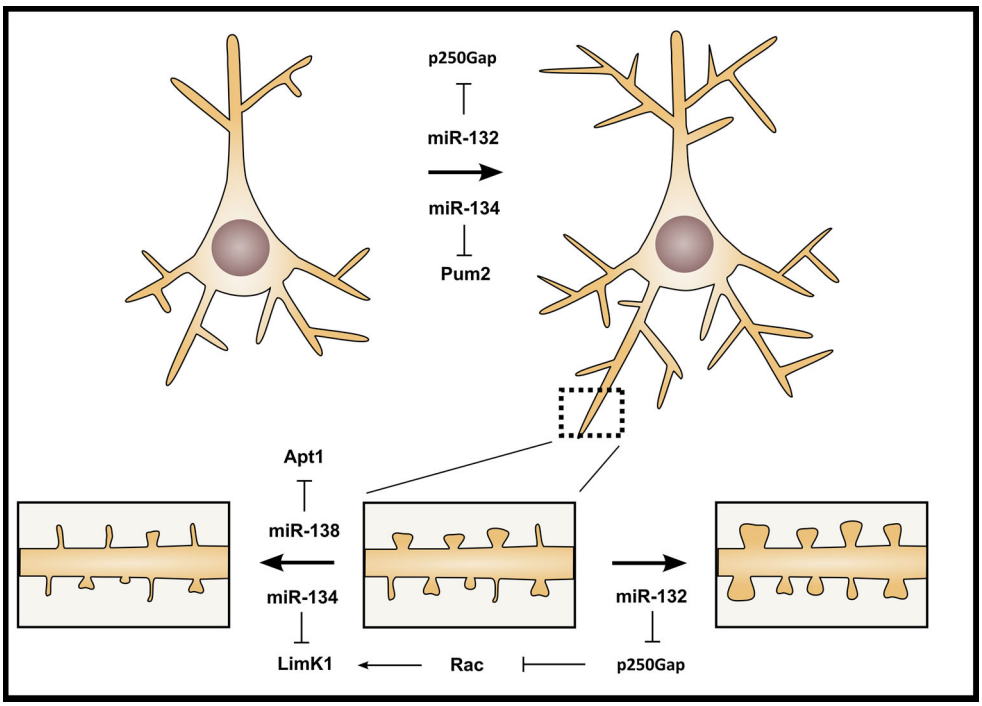

Fig. 2 Regulation of dendritic complexity and spine morphogenesis by the "miRNA troika". Dendritic complexity and spine morphology are regulated by miRNAs. Increased miR-132 and miR-134 levels promote neurite growth and branching by targeting p250GAP and Pum2, respectively. Furthermore, dendritic spine morphogenesis is positively regulated by miR-132 through indirect activation of LimK1, whereas the spine size is negatively regulated by miR-134 through inhibition of LimK1 and by miR-138 through inhibition of Apt1

Table 2 Summary of all miRNAs with validated dendritic targets in rodents

MicroRNA	Target(s)	Relevance	Disease implication	Reference(s)
miR-9	BK channel isoforms	Responsiveness to alcohol	Alcohol addiction	[159]
miR-29a/b	Arpc3	Dendritic spine morphology	Several forms of addiction	[160]
miR-124	RhoG	Dendrite complexity		[161]
miR-125a	PSD-95	Dendritic spine morphology	Fragile X Syndrome	[33]
miR-125b	NR2A	Synapse structure and function	Fragile X Syndrome	[57]
miR-128	Szdr1/D4ertd22e, Pea15a, TARPP/Arpp21	Dendritic excitability	Epilepsy	[162]
miR-129	Kv1.1	Dendritic excitability		[163]
miR-132	p250Gap	Dendrite complexity and dendritic spine morphology	See Table 1 for details	[23, 24, 91]
miR-134	Limk1, Pum2	Dendrite complexity and dendritic spine morphology	See Table 1 for details	[22, 63]
miR-135	complexin-1/2	NMDA-induced		[164]
		Spine remodeling		
miR-137	Mib1	Dendrite complexity	Schizophrenia	[165–169]
	CACNA1C		Huntington's disease	
	CSMD1		Intellectual disability	
	C10orf26			
	TCF4			
miR-138	Apt1	Dendritic spine morphology	See Table 1 for details	[56]
miR-146-5p	MAP1B	AMPA receptor endocytosis	Rett syndrome	[170, 171]
miR-181a	GluA2	Synapse structure and function	Cocaine addiction	[172, 173]
miR-188	Nrp-2	Dendritic spine density and synapse function		[174]
miR-191	Tmod 2	NMDA-induced		[164]
		Spine remodeling		
miR-219	CamKIIγ	NMDA receptor-mediated neurobehaviour	Schizophrenia	[175]
miR-375	HuD	Dendrite density		[176]

Conclusions and future perspectives

Synaptic plasticity is a key mechanism enabling neurons to adapt to activity-induced changes by specific regulation of individual synapses, which requires local fine-tuning of protein synthesis. Dendritic miRNAs are well-suited for regulating this process, as implied by the activity-dependent regulation of miRNA expression and function, as well as the reversibility of translational repression. Research during the past decade has helped to elucidate an entire network of dendritic miRNAs and revealed several intersection points between various miRNA pathways. Nevertheless, further investigation is required to assess whether the findings concerning miRNA function derived from cell-culture models can be recapitulated by in vivo studies. As sophisticated animal models with altered miRNA expression patterns are being engineered, it can be expected that data concerning the physiological impact of miRNAs in the intact brain will become available in the near future. Moreover, the regulation of compartmentalized gene expression by miRNAs is an important topic that will greatly benefit from novel approaches that allow the visualization of gene expression in space and time at unprecedented resolution. The post-transcriptional control of miRNA biogenesis and activity in neurons likely represents another important regulatory layer that must be examined in greater detail. Finally, numerous reports have implicated the miRNA pathway in neurological and neuropsychiatric diseases such as epilepsy, mental retardation or autism. Given that these links are substantiated in future studies, this will likely open a whole molecular treasure chest for novel treatment options. Potential therapeutic approaches could involve miRNA inhibition by miRNA sponges, decoys or antagomiRs. In addition, increasing low endogenous miRNA levels by overexpression might be beneficial for some pathologic conditions. Future studies will have to systematically test the effectiveness of such tools in vivo in models of neurological and neuropsychiatric diseases. In conclusion, dendritic miRNAs are crucial regulators of local gene expression in neurons. Undoubtedly, future studies on brain miRNA biology promise to expand our knowledge of the complex molecular mechanisms underlying higher cognitive functions.

Acknowledgments We thank Anna Antoniou for valuable comments on the manuscript. Research in the Schratt laboratory is funded by grants from the DFG (SFB593, SPP1738), the ERC (Starting Grant "Neuromir") and the EU FP7 HEALTH ("EpiMirna").

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