Neuroscience Letters 466 (2009) 55–62

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Mini-review

microRNA involvement in developmental and functional aspects of the nervous system and in neurological diseases

Mette Christensen[a,b], Gerhard M. Schratt[a,*]

[a] Interdisziplinäres Zentrum für Neurowissenschaften, SFB488 Junior Group, Universität Heidelberg, and Institut für Neuroanatomie, Universitätsklinikum Heidelberg, Im Neuenheimer Feld 345, 69120 Heidelberg, Germany
[b] Wilhelm Johannsen Center for Functional Genome Research, Department of Cellular and Molecular Medicine, The Panum Institute, University of Copenhagen, Blegdamsvej 3, 2200 Copenhagen N, Denmark

ARTICLE INFO

Article history:
Received 16 February 2009
Received in revised form 27 March 2009
Accepted 20 April 2009

Keywords:
microRNAs
Nervous system
Differentiation
Plasticity
Neurological diseases

ABSTRACT

microRNAs, small non-coding RNAs that regulate gene expression at the post-transcriptional level, are emerging as important regulatory molecules involved in the fine-tuning of gene expression during neuronal development and function. microRNAs have roles during neuronal stem cell commitment and early differentiation as well as in later stages of neuronal development, such as dendritogenesis and synaptic plasticity. A link between microRNAs and neurological diseases, such as neurodegeneration or synaptic dysfunction, is becoming increasingly clear. This review summarizes the current knowledge of the function of microRNAs in the developing and adult nervous system and their potential contribution to the etiology of neurological diseases.

Introduction

The discovery of microRNAs (miRNAs) has introduced an important new layer of regulatory control of gene expression. miRNAs are short non-coding RNAs, about 21 nucleotides (nt's) long, that modulate gene expression at the post-transcriptional level by guiding cellular machinery to the 3′-untranslated region (3′-UTR) of specific messenger RNAs (mRNAs) to control their expression. Since the biogenesis and mechanism of action of miRNAs has been extensively described in other reviews [6,9], it will only be briefly discussed here. Most miRNAs are transcribed by polymerase II, although a few human miRNAs have been shown to be transcribed by polymerase III [8]. The primary transcript (pri-miRNA) can be up to several thousand nt's long and contains internal hairpin structures. Within the nucleus, the pri-miRNA is processed by the RNase III enzyme Drosha, resulting in a ~70 nt long hairpin precursor miRNA (pre-miRNA) containing a 2-nt 3′overhang. This overhang is recognized by Exportin-5, which transports the pre-miRNA into the cytoplasm. In the cytoplasm, the pre-miRNA is further cleaved by the RNase III enzyme Dicer. This results in the formation of an intermediary miRNA:miRNA* duplex consisting of the ~21 nt mature miRNA and its star sequence, miRNA*. Following unwinding of the miRNA duplex by a helicase, the mature miRNA is incorporated into the RNA-induced silencing complex (RISC), whereas the miRNA* is usually degraded. Binding of a miRNA to its target mRNA requires both RISC and the presence of Argonaute (Ago) proteins. miRNA target recognition usually involves strong base-pairing between residue 2–8 at the 5′-end of miRNAs, the so-called seed sequence, and complementary sequences in the 3′-UTR of the target mRNA. Depending on the degree of complementarity between the miRNA and its target, the target mRNA can either be cleaved and degraded or translationally repressed. Perfect complementarity induces degradation of the mRNA, whereas non-perfect complementarity results in translational inhibition. In animals, miRNA silencing of gene expression is predominantly mediated by translational blockade. To date, the mechanisms behind translational inhibition are elusive. Regulation at the step of translational initiation is believed to be the main mechanism to block translation, although evidence for regulation at post-initiation steps has also been put forward [51]. The miRNA induced translational inhibition appears to be reversible in a few instances [7,55], rendering the miRNA mediated regulation dynamic and responsive to specific cellular needs.

Vertebrate miRNA genes either occur as isolated genes or are located in large miRNA clusters that are coordinately transcribed as polycistronic primary transcripts [15]. Non-clustered miRNA genes can be transcribed from their own promoter, though 40% and 10% of human and mouse miRNA genes are located within introns and exons, respectively, of non-protein-coding or protein-coding transcripts and expressed along with their host gene [77].

* Corresponding author. Tel.: +49 6221 566210; fax: +49 6221 567897.
E-mail address: schratt@ana.uni-heidelberg.de (G.M. Schratt).

0304-3940/$ – see front matter © 2009 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.neulet.2009.04.043

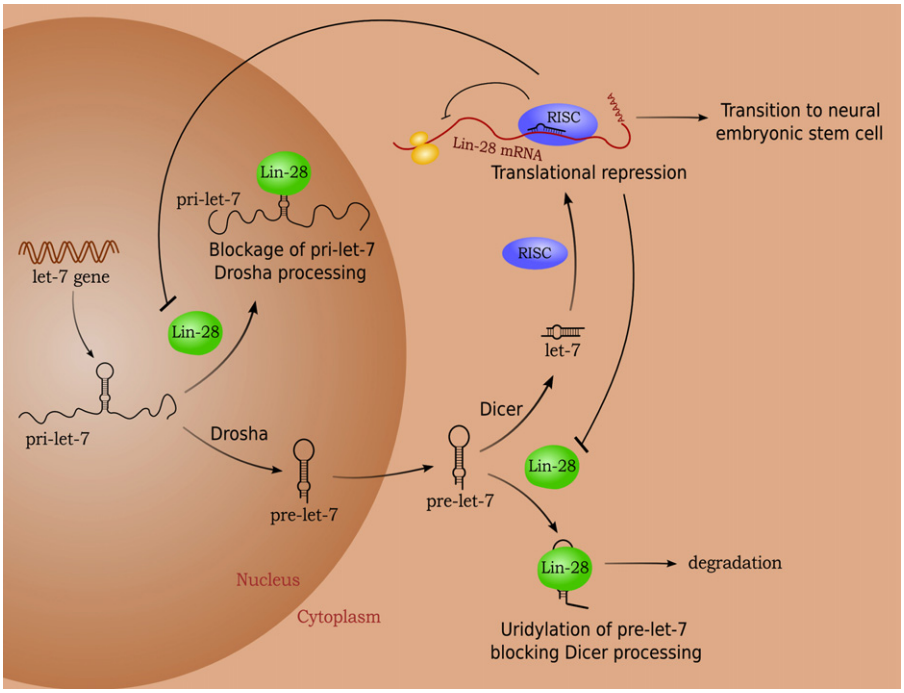

Fig. 1. Working model for the role of let-7 in neural cell lineage specification. Transition of embryonic to neural stem cells is controlled by let-7. The level of let-7 is regulated by a double-negative feedback loop between let-7 and Lin-28. Lin-28 protein suppresses let-7 at the post-transcriptional level, thereby maintaining embryonic stem cell identity. Translational inhibition of Lin-28 mRNA by let-7 allows processing of let-7, resulting in neural stem cell commitment. Lin-28 suppression of let-7 processing can be achieved by two mechanisms: (1) in the nucleus, Lin-28 binds to the loop of the hairpin structure in the pri-let-7 transcript, thereby blocking Drosha processing; (2) in the cytoplasm, Lin-28 induces uridylation of pre-let-7. Uridylated pre-let-7 is not recognized by Dicer and undergoes degradation.

miRNAs are very abundant in multicellular organisms and influence the expression of many protein-coding genes. To date, approximately 700 miRNAs have been described in the human genome [23] and the number is continuously expanding. Each miRNA has been estimated to target up to a few hundred target genes [33] and, altogether, miRNAs have been suggested to regulate as much as one third of the protein coding genes in animals [38]. miRNAs are divided into families based on similarities in their seed sequences. One-third of miRNA families are highly conserved across species, and as much as 60% conservation between mouse and human mature miRNAs is observed [52]. miRNAs have been implicated in diverse cellular processes such as developmental timing, apoptosis, metabolism, myogenesis and cardiogenesis [31].

Taking into account the high complexity of the brain and its neuronal circuits, it comes as no surprise that miRNAs are emerging as essential regulators of the development and function of the nervous system. miRNA research is still a relatively nascent field, and detailed mechanisms on miRNA involvement in the regulatory circuits of the nervous system are just beginning to be unveiled. This review presents an overview of the current knowledge about the involvement of miRNA regulatory pathways in the function of the developing and adult nervous system and in neurological diseases.

Role of Dicer and microRNAs in the nervous system

The brain is a rich source of miRNAs and several studies using miRNA expression profiling reveal that a significant fraction of miRNAs are enriched or specifically expressed in the nervous system [18,36], and that their expression is precisely regulated during brain development [34,46]. This initially indicated an important role of miRNAs in brain development, neuronal differentiation and regulation of brain and neuron specific gene expression. Genomic *Dicer* ablation results in the absence of all mature miRNAs and has been used as a valuable tool to study the general involvement of miRNA regulatory pathways in the nervous system. Severe brain morphogenesis deficits are observed in zebrafish *Dicer* knockout mutants. Lack of Dicer can be rescued by miR-430, a large family of miRNAs expressed during early zebrafish development, implicating an essential role for this miRNA family during brain development [22]. In mice, *Dicer* ablation causes neurodegeneration and cell death of subpopulations of neurons, such as dopamine neurons in the midbrain [29], postmitotic Purkinje cells of the cerebellum [54] and neocortical neurons [17]. In addition, loss of Dicer in cortex and hippocampus affects cellular and tissue morphology, axonal pathfinding and apoptosis [16]. This indicates that miRNAs are important in such diverse processes as neuronal and tissue morphogenesis, neuronal survival and possibly neurodegenerative diseases. *Dicer* silencing in neocortical progenitors impairs neuronal differentiation [17] and results in abnormal terminal differentiation of developing olfactory progenitors. Inhibiting the miR-200 family alone, a family of miRNAs highly expressed in olfactory tissue, phenocopies the abnormal terminal differentiation in olfactory progenitors [14]. As a whole, these results indicate a central role for miRNAs during neuronal differentiation.

The studies using *Dicer* mutants have revealed undoubtedly important roles for miRNAs in many diverse aspects of the nervous system. Nevertheless, the ablation of *Dicer* does not reveal anything about the function of individual miRNAs. The remaining of this review is focused on the impact of individual miRNAs on developmental and functional aspects of the nervous system.

microRNAs in neural cell lineage specification and differentiation

A number of studies have identified the importance of miRNA regulatory pathways in early events of neuronal development, such as neural stem cell commitment, differentiation and neurite outgrowth. let-7 was originally discovered in *Caenorhabditis elegans* as a regulator of developmental timing through the regulation of cell proliferation and differentiation [10]. This miRNA is highly

expressed in brain tissues of diverse organisms, such as zebrafish and mouse [36,71]. let-7 expression is low in undifferentiated embryonic stem cells, but increases upon differentiation to the neural lineage [53,73]. In the process of neural stem cell commitment, let-7 is part of a double-negative feedback loop where the level of let-7 expression is believed to control the embryonic to neural embryonic stem cell transition (Fig. 1) [53]. Although mature let-7 is not expressed in undifferentiated embryonic stem cells, these cells nevertheless express pre-let-7, suggesting a post-transcriptional regulation of let-7 expression. One candidate regulator is Lin-28 [26,47,53,65], a protein best known for its involvement in developmental timing in *C. elegans* [10], but which has recently been shown to be involved in reprogramming of human somatic cells to pluripotent stem cells [75]. The Lin-28 mediated negative regulation of let-7 expression occurs through inhibition of let-7 processing events. Evidence for two mechanisms for the Lin-28 mediated inhibition of let-7 processing has been accumulated. Firstly, Lin-28 binds to the loop region of the hairpin structure in the pri-let-7 transcript, thereby blocking Drosha processing [47]. Secondly, Lin-28 induces uridylation of pre-let-7 at its 3′end, resulting in a failure of the precursor to undergo Dicer processing [26]. During neural cell lineage specification, Lin-28 and let-7 collaborate in controlling maturation of let-7. Lin-28 is downregulated by let-7 allowing processing of pri/pre-let-7, whereas suppression of let-7 by Lin-28 leads to upregulation of Lin-28 and loss of pri/pre-let-7 processing [53].

A study of miRNA involvement in neuron differentiation revealed an important role for the brain-specific miRNAs, miR-9 and miR-124. These miRNAs display an increased expression during neurogenesis. Overexpression of the two miRNAs causes a reduction in astrocyte lineage differentiation in culture, whereas inhibition of miR-9 alone or in combination with miR-124, causes reduced numbers of neurons [35]. In addition, increased expression of miR-125a and -b is observed during differentiation of embryonal carcinoma cells into neurons. A regulatory target of both miR-125 family members is the mammalian Lin-28 and the two miRNAs contribute to the observed repression of Lin-28 in differentiated neurons [72]. In mouse, miR-9 is abundantly expressed in the cortex during development where it supports proper differentiation of Cajal-Retzius cells in the medial pallium. This effect is mediated through the regulation of *Foxg1*, a gene involved in sustaining the undifferentiated state of Cajal-Retzius cells [56]. Finally, miR-133b controls differentiation of midbrain dopaminergic neurons [29], a topic that will be described in detail later upon the discussion of Parkinson's disease.

miR-124 is a neuron specific miRNA important for neuronal development [59]. The major role of miR-124 is repression of non-neuronal genes in neurons, thereby maintaining their cellular identity [11,41,64]. The miR-124 pathway interacts with the neuron-restrictive silencing factor/RE-1 silencing transcription factor (NRSF/REST) pathway that suppresses neuronal gene expression in non-neuronal cells. NRSF/REST is downregulated during the transition from progenitors to post-mitotic neurons. Since *miR-124* transcription is NRSF/REST dependent, this allows expression of miR-124, which in turn represses the non-neuronal genes. Interestingly, a target of miR-124 is the small-C-terminal domain phosphatase 1 (SPC1), an anti-neuronal factor implicated in the function of the NRSF/REST complex [64]. In addition, miR-124 can induce the expression of neuronal specific genes through regulation of the RNA-binding protein PTBP1, a repressor of alternative splicing that promotes the production of neuron-specific transcripts. PTBP1 displays high expression levels in non-neuronal cells but not in neuronal cells, presumably due to post-transcriptional downregulation exerted by miR-124. The targeting of PTBP1 by miR-124 allows neuronal-specific alternative splicing and miR-124 enhanced differentiation into neurons [44].

Apart from the role of miR-124 in silencing non-neuronal genes and promoting expression of neuronal genes, miR-124 is involved in neurite outgrowth in differentiating mouse embryonal carcinoma cells. The downstream effectors of miR-124 in this paradigm are Rac1 and Cdc42, small GTPases of the Rho family that regulate microtubule and actin filament dynamics in various cell types. This implicates a role for miR-124 in regulating genes controlling cytoskeleton reorganization [76]. Another miRNA regulating neurite growth is miR-388. The gene for miR-388 is located within an intron of the apoptosis-associated tyrosine kinase (*Aatk*), a kinase essential for neuronal differentiation and neurite extension. During development of neurites, AATK and miR-388 are co-expressed and both molecules are required for optimal neurite growth. In addition, miR-388 silences gene products that are negative regulators of neuronal differentiation, thereby working along with AATK to promote neural differentiation [5].

microRNAs in brain development

Although a large percentage of known miRNAs are present in the brain, not much is known about the role of miRNAs in brain development. Nevertheless, two recent studies indicate important new roles of miRNAs in neural tube closure and brain patterning. Mice with a mutated *Mlin41* gene display defects in neural tube closure during development and embryonic lethality. *Mlin41* is an orthologue of *C. elegans Lin-41*, a let-7 target gene acting in the regulatory control of hypodermal cell differentiation during transition of *C. elegans* larval to adult state [58,63]. *In vitro*, let-7 and miR-125 have been shown to regulate Mlin41 expression through cognate binding sites in the 3′-UTR. Downregulation of Mlin41 in the developing mouse embryo around E9.5 goes hand in hand with increased expression of let-7 and miR-125 in an overlapping pattern [45], supporting a role for the let-7/miR-125/Lin-41 regulatory circuit in neural tube development.

In zebrafish, miR-9 has been postulated to define the limits of the midbrain–hindbrain boundary (MHB), a long-lasting organization center of the neural tube involved in mid- and hindbrain (MH) development. The MHB contains progenitor cells and contributes neurons to MH. Ectopic induction of neurogenesis within the MHB results in premature differentiation and a failure in maintaining MHB activity. Important components for the maintenance and activity of the MHB are fibroblast growth factor 8 (Fgf8) signaling, including fibroblast growth factor receptor 1 (FgfR1), and Her transcription factors, inhibitors of neurogenesis in the MHB. Strikingly, miR-9, otherwise a highly expressed miRNA throughout the brain, is not expressed in the MHB. Ectopic expression of miR-9 in the MHB promotes neurogenesis, thereby leading to a loss of the MHB. This effect of miR-9 is mediated by downregulation of Fgf8, FgfR1 as well as Her5 and -9, all components of the regulatory apparatus involved in maintenance and activity of the MHB. miR-9 promotes neurogenesis in MH and miR-9 expression in the surrounding regions of the MHB could help to define the limits of the MHB and also the MHB progenitor pool [37]. Together, these results suggest a new role for miRNAs in patterning of the brain. However, more studies will have to be performed to reveal a more complete picture of the involvement of miRNAs in promoting normal brain development.

microRNAs in synaptic plasticity

The adult brain contains a highly organized network of neurons contacting each other through synapses. Modulation of synaptic strength and structure is believed to be the fundamental mechanism underlying memory formation [4]. New protein synthesis is required for certain forms of long-term memory establishment

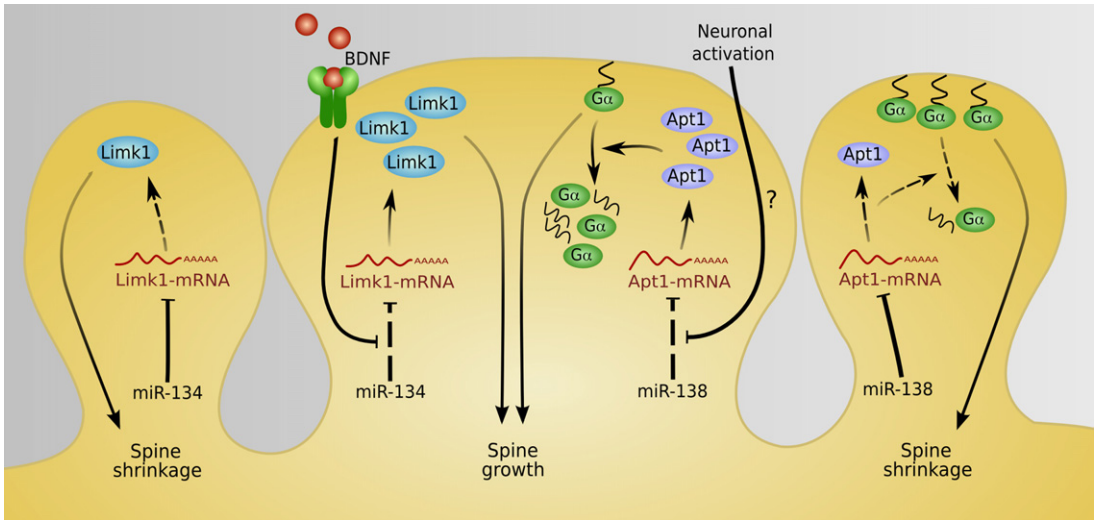

Fig. 2. Role of miRNAs in local dendritic protein synthesis and spine morphogenesis. At the synapse, miR-134 inhibits translation of Limk1 mRNA (left) and miR-138 inhibits translation of Apt1 mRNA (right), thereby restricting dendritic spine growth. The effect of miR-138 on spine morphogenesis is most likely caused by excessive palmitoylation of Gα. Middle: BDNF relieves the inhibitory effect of miR-134 on Limk1 mRNA translation by a yet unknown mechanism. The enhanced synthesis of Limk1 protein results in dendritic spine growth. A similar synaptic activation might relieve miR-138 mediated translational repression of the Apt1 mRNA. This in turn would result in increased depalmitoylation of Gα and dendritic spine growth.

and in some cases newly synthesized proteins derive from the local translation of mRNAs within neural processes. A subset of these mRNAs is located in the dendritic shaft and in spines [61], small actin-rich protrusions from dendrites and the primary sites of excitatory synaptic contact. Several recent findings suggest that miRNAs function in the translational control of dendritically localized mRNAs. Both miRNAs and pre-miRs have been detected in synaptoneurosomes [43,57], biochemical preparations of synaptic membranes. In addition, Dicer localizes to dendritic spines. There, Dicer appears to be activated upon neuronal stimulation through regulated cleavage by the calcium-dependent protease calpain [42]. This raises the interesting possibility that synaptic stimulation might result in the activation of Dicer. Activated Dicer in turn could process dormant pre-miRs located at the synapse to functional mature miRNAs, thereby regulating local mRNA translation in an activity-dependent manner. A study in *Drosophila* genetically links the miRNA pathway to local protein synthesis and memory formation. Armitage, a component of the RISC pathway is found at mushroom body synapses and locally degraded upon neural activation that leads to the formation of a long-term memory trace. This in turn results in local synaptic translation of calcium/calmodulin dependent kinase II mRNA and synaptic potentiation. Thus, synaptic protein synthesis and stable memory formation in this example is under degradative control of the RISC pathway [3].

The involvement of miRNAs in the regulatory control of local protein synthesis at the mammalian synapse was provided by a study of the brain-specific miRNA, miR-134, in cultured hippocampal neurons. miR-134 is located in the synaptodendritic compartment where it co-localizes and inhibits translation of Limdomain containing protein kinase 1 (Limk1), a regulator of actin filament dynamics involved in dendritic spine morphology. The downregulation of Limk1 protein synthesis restricts the growth of dendritic spines, thereby limiting excitatory synapse development. Interestingly, the interaction between Limk1 mRNA and miR-134 is relieved by exposure of neurons to brain-derived neurotrophic factor (BDNF), a neurotrophin secreted in response to synaptic stimulation (Fig. 2) [55]. The mechanism underlying the switch between translational inhibition and activation of Limk1 by miR-134 is currently unknown.

miR-138 is another brain-specific miRNA that we found to be located in dendrites and to negatively regulate spine size. miR-138 inhibits the expression of Acyl protein thioesterase 1 (APT1), a depalmitoylating enzyme controlling the palmitoylation status of proteins at the synapse and hence their membrane association. Several signaling molecules are substrates for APT1, notably G protein alpha subunit (Gα), and our results suggest that reduced depalmitoylation of Gα could underlie the miR-138 spine phenotype (Fig. 2) [57].

Fragile X syndrome (FXS) is an inherited mental retardation caused by massive expansion of CGG trinucleotide repeats within the regulatory region of the fragile X mental retardation (*Fmr1*) gene, resulting in the loss of fragile X mental retardation protein (FMRP) expression [39]. Abnormal dendritic spines are observed in FXS patients and *Fmr1* knock-out mice, indicating that FMRP could regulate synaptic plasticity [48]. FMRP is an RNA binding protein that acts as a suppressor of local mRNA translation in the synaptodendritic compartment [19,40,70]. In addition, FMRP plays a role in the transport of mRNAs into the dendritic compartment of neurons [2]. In *Drosophila*, FMRP has been found to interact with miRNAs, Dicer and Ago1, and the interaction between Ago1 and FMRP is crucial for synaptogenesis [12,27]. Ago1 associates with, and is believed to stabilize, Dicer/pre-miR complexes [49]. Recently, the absence of FMRP has been reported to result in the disruption of the Dicer-Ago1 association as well as reduced processing of pre-miRs, suggesting a new role of FMRP in the regulation of miRNA biogenesis [74]. Therefore, FMRP could affect the miRNA pathway at two stages: miRNA processing and miRNA mediated translational regulation. Interestingly, the observed phenotype of FMRP inactivation on spine morphology resembles that of miR-134 and miR-138 overexpression. It will be interesting to find out whether the absence of FMRP impairs the biosynthesis and/or activity of these miRNAs during spine development.

N-methyl-D-aspartate (NMDA) glutamate receptors are regulators of synaptic plasticity. Disruption of NMDA-mediated glutamate signaling has been linked to psychiatric disorders like schizophrenia and, interestingly, has been shown to result in reduced levels of the brain-specific miR-219 in the prefrontal cortex of mice. miR-219 has recently been shown to be a negative regulator of calcium/calmodulin-dependent protein kinase II γ subunit (CaMKII γ) expression, a downstream mediator of NMDA-R signaling. The reduced level of miR-219 could represent a compensatory mechanism for NMDA-R hypofunction by increasing the levels

of CaMKII dependent signaling [32]. In addition, a study of the 22q11.2 microdeletion has linked the miRNA regulatory pathway to schizophrenia. The microdeletion, which is associated with a high risk of developing schizophrenia, includes the gene encoding Dgcr8. Dgcr8 is involved in miRNA biogenesis through its interaction with Drosha. An alteration of miRNA biogenesis is observed in *Dgcr8* deficient mice and hypothesized to contribute to the behavioral and neuronal deficits caused by the 22q11.2 microdeletion. *Dgcr8* deficient mice have reduced number and size of hippocampal dendritic spines, decreased dendritic complexity and display affected cognitive and behavioral performances [60].

Together, these recent results indicate a previously unknown complexity of miRNA function in synaptic plasticity. It is conceivable that miRNAs such as miR-134 and miR-138, in collaboration, fine tune spine morphogenesis in response to different synaptic stimuli. An important question is how widespread the miRNA mediated control of synaptic plasticity is – are more miRNAs involved in this process through the regulation of additional targets involved in spine morphogenesis? Furthermore, it is still unknown how the miRNAs are transported to the synapse. miRNAs could be transported to the synapse bound to their target mRNAs or by means of RNA binding proteins involved in dendritic transport of RNA, one such candidate being FMRP. More studies have to be performed to answer these questions.

Activity-dependent regulation of microRNAs in the nervous system

Activity-dependent programs of gene expression are important for processes like dendritic outgrowth, synaptic maturation and elimination, and plasticity in the adult brain [21]. The expression of miRNAs has in a few instances been shown to be driven by neuronal activation resulting in activity-dependent miRNA regulation of target genes. Recently, we found that miR-134 is not only regulated locally at the synapse, but also globally within the neuron by an activity-dependent transcriptional program. The *miR-134* gene is localized in a large miRNA cluster within the *Gtl2/Dlk1* domain, consisting of ~50 brain-specific miRNAs. Transcription of the miR cluster is activated after neuronal activation in a Myocyte enhancing factor 2 (Mef2) dependent manner. The Mef2 induced expression of miR-134 is required for activity-dependent dendritic outgrowth of hippocampal neurons and this effect is likely mediated by miR-134 dependent inhibition of the translational repressor Pumilio2 (Pum2) [20].

Another miRNA transcribed in an activity-dependent manner is the brain-specific miR-132, which is regulated by the cAMP response element-binding (CREB) protein pathway. CREB is a key regulator of neurite outgrowth, though few CREB targets have been linked to plasticity. A global screen for CREB targets identified *miR-132* as a target and, subsequently, miR-132 was shown to promote neurite outgrowth. This effect is mediated by the downregulation of the Rho family GTPase-activating protein, p250GAP, itself a negative regulator of neurite outgrowth [66,69]. Furthermore, miR-132 has been linked to Rett syndrome, an X-linked neurodevelopmental disease caused by mutations in the gene encoding methyl-CpG binding protein (MeCP2). Since both increase and decrease of MeCP2 cause neurodevelopmental defects, the level of MeCP2 has to be within a narrow range to allow normal neuronal development. Expression of MeCP2 is negatively controlled by miR-132, presumably preventing MeCP2 levels from being deleteriously high during neuronal maturation. This further suggests that abnormal expression of miR-132 in Rett syndrome patients could contribute to the deregulated MeCP2 protein levels observed in these patients [30].

Modulation of the circadian clock, an internal timekeeping mechanism allowing most organisms to adapt their physiological and behavioral processes to a cyclic 24-h world, has also been shown to involve CREB-dependent transcription of *miR-132 in vivo*. The circadian clock, which is controlled by the suprachiasmatic nuclei (SCN), is entrained or reset by light. Expression of miR-132 is induced by light in a CREB dependent manner and involved in attenuation of the entrainment effects of light. Another brain-specific miRNA, miR-219-1, is targeted by the molecular clock itself via CLOCK and BMAL1, transcription factors controlling the circadian rhythm. miR-219-1 modulates the length of the circadian days [13].

Activity-dependent transcription of miRNAs could be a feedback mechanism to scale the activity of different neuronal circuits to the magnitude of synaptic stimulation. Therefore, fine-tuning of gene expression in response to neural activity could be considered as a homeostatic mechanism. It will be important to identify the neural circuits using miRNA-controlled homeostasis *in vivo*.

microRNAs in neurodegeneration

Our knowledge of the involvement of miRNAs in neurodegeneration mostly originates from the already covered studies of *Dicer* ablation. These studies revealed a necessity of miRNAs for the survival of specific types of neurons in the brain. In addition, studies in the context of human neurodegenerative diseases (NDs) that uncovered deregulated miRNA expression strongly suggest a contribution of individual miRNAs to disease etiology. However, evidence for a direct causal involvement of miRNAs in NDs is still missing. For example, it is not known if the disease linked miRNAs can account for the dramatic phenotypes observed in NDs, or if their misregulation is simply a byproduct of other cellular processes affected in the disease. Before summarizing some of the currently known links between the miRNA regulatory pathway and human NDs, it is worth mentioning a study from *Drosophila* which links miRNA regulation to the control of brain apoptosis. *Drosophila* miR-8 regulates the expression of atrophin, a transcriptional corepressor associated with histone deacetylase activity. *miR-8* mutants display an elevated expression of atrophin, which in turn leads to increased apoptosis in the brain and behavioral defects. Overexpression of miR-8 similarly increased lethality indicating a role of miR-8 in fine-tuning the expression levels of atrophin within a narrow window to prevent neurodegeneration in the brain. Interestingly, the regulatory relationship between miR-8 and atrophin orthologs is conserved in mammals and could therefore also be relevant for neurodegeneration in humans [28].

Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD) are NDs caused by excessive neuronal death in the diseased brain. A hallmark of AD is the formation of insoluble plaques of amyloid β (Aβ)-peptide in the brain. The Aβ peptides derive from the proteolytic cleavage of β-amyloid precursor protein (APP) by beta-site APP-cleaving enzyme (BACE) [62]. *In vitro*, miR-20a, miR-17-5p and miR-106b have the capacity to regulate APP expression. Interestingly, miR-106b displays reduced expression in the brain from sporadic AD patients, possibly linking miRNA misregulation of APP to an elevated production of Aβ [24]. Increased levels of BACE1 correlate with Aβ accumulation, and impaired expression of BACE1 in response to perturbation of the miRNA pathway might therefore contribute to AD etiology. miR-107 levels are decreased in AD patients compared to healthy individuals, even at early stages of disease progression. Indeed, increased levels of BACE1 mRNA correlate with decreased miR-107 levels during AD progression in patients. Interestingly, the 3′-UTR of BACE1 contains multiple predicted miR-107 target sites [68]. In addition, the *miR-29a/b-1* cluster has been identified as a potential major suppressor of BACE1 translation. A clear correlation between increased BACE1 protein levels and decreased miR-29a/b-1 has been observed in patients with sporadic AD. *In vitro*, miR-29a and miR-29b-1 have

the capacity to regulate BACE1 protein levels. In addition, in cell culture experiments, suppression of miR-29a/b-1 leads to increased Aβ production further supporting an involvement of miR-29a and miR-29-b-1 in the development of AD [25].

Recent results indicate that miRNA perturbation might also contribute to the development of sporadic PD, a disease characterized by the loss of dopaminergic neurons (DNs) in the midbrain. *In vivo*, inactivation of *Dicer* results in loss of midbrain DNs, a phenotype resembling that of PD. Increased cell death upon *Dicer* ablation could also be observed *in vitro*, and could be rescued by introduction of low molecular weight RNA species that had been purified from wild type cells. These results argue that the phenotype is caused by the lack of miRNAs and not by miRNA unrelated functions of Dicer. miR-133b is enriched in the DNs of the midbrain of healthy individuals but diminished in the midbrain tissue of PD patients. *In vitro*, miR-133b has been shown to be necessary and sufficient for the differentiation of DNs. Mechanistically, miR-133b is part of a negative feedback loop controlling DN differentiation. Transcription of *miR-133b* is induced by Pitx3, a transcriptional activator inducing midbrain DN gene expression, and Pitx3 in turn is translationally regulated by miR-133b [29]. Together, this strongly suggests that miR-133b is a regulator of DN differentiation and possibly involved in PD etiology. The exact genetic mutations leading to PD are still unknown, though several single nucleotide polymorphisms (SNPs) found in PD families have been linked to disease formation. One of these SNPs is located in the *Fgf20* gene within a predicted binding site for miR-433. The SNP disrupts binding of miR-433, thereby resulting in increased translation of Fgf20. Elevated levels of Fgf20 protein in turn enhance expression of α-synuclein, a protein that accumulates in PD brain forming cytoplasmic inclusions termed Lewy bodies. Since overexpression of α-synuclein is known to cause PD deregulated Fgf20 levels in PD patients link the miRNA pathway to PD formation [67]. These findings illustrate that impaired binding of miRNAs to crucial target genes due to SNPs can have severe pathological consequences. This notion is supported by the recent discovery of a SNP that impairs miRNA binding to the Tourette's syndrome gene *Slitrk1*, although the relevance of this finding is uncertain due to the low incidence of these mutations [1].

HD is a ND primarily caused by a trinucleotide repeat expansion of the gene encoding Huntingtin (Htt). At the molecular level, HD is characterized in part by impaired transcriptional progression in striatum and cortical regions. In healthy individuals, the transcriptional repressor protein REST is primarily found in the cytoplasm through interaction with Htt. In HD patients, REST is incapable of binding Htt and accumulates in the nucleus. In the nucleus, REST recruits corepressors, including the REST corepressor 1 (CoREST), to inactivate neuron-specific genes. *In vitro*, it has been established that miR-9 targets REST while miR-9* targets coREST. Expression of miR-9/9* is decreased early in HD disease progression, indicating that increased expression of REST and coREST in HD patients could be due to decreased miRNA-9/9* mediated translational inhibition. This in turn would result in inappropriate repression of neuron-specific genes. In addition, reduced REST expression results in enhanced expression of miR-9/9*, thereby constituting a negative feed back loop between REST and the REST-regulated miRNAs [50].

Conclusion

miRNA research is still a relatively new field and our current knowledge of the regulatory mechanisms exerted by miRNAs in the development and function of the nervous system is still very limited. However, it is apparent that miRNAs have important roles in a plethora of aspects of the CNS, like neural specification and differentiation, dendritogenesis, and synaptic plasticity. Most likely, more functions of miRNAs in the CNS will be revealed in the future. A more detailed picture of the number of regulatory circuits involving miRNAs in neurons and the brain is required to completely understand the importance of miRNAs in the function and development of the nervous system. The impact of an individual miRNA is potentially much higher than currently known due to their capacity to regulate multiple target genes, and the question arises how miRNAs manage to regulate a specific physiological pathway when displaying the capacity to interact with hundreds of target mRNAs. Simultaneously, in this light, it will be important to understand the regulatory pathways that control the spatial and temporal expression of miRNAs as well as the interaction of miRNAs with their target mRNAs in specific neuronal subtypes of the brain. The dynamic remodeling of miRNA complexes in response to activity, as illustrated by the LimK/miR-134 interaction, is also an important topic for future studies. Finally, links between miRNAs and disease etiology are appearing, though it is uncertain if aberrant miRNA activity are causing the neurological diseases or if they are simply a consequence of the disease. Notwithstanding, the miRNA pathway could be a possible target in the development of new therapeutic approaches in the treatment of neurological diseases.

Acknowledgements

This work was supported by grants from the Danish Medical Research Council (M.C.), the Deutsche Forschungsgemeinschaft (SFB488; G.M.S.), the National Institute on Drug Abuse (1R21DA025102-01; G.M.S.), and the Human Frontier Science Program (Career Developmental Award; G.M.S.).

References

[1] J.F. Abelson, K.Y. Kwan, B.J. O'Roak, D.Y. Baek, A.A. Stillman, T.M. Morgan, C.A. Mathews, D.L. Pauls, M.R. Rasin, M. Gunel, N.R. Davis, A.G. Ercan-Sencicek, D.H. Guez, J.A. Spertus, J.F. Leckman, L.S. Dure IV, R. Kurlan, H.S. Singer, D.L. Gilbert, A. Farhi, A. Louvi, R.P. Lifton, N. Sestan, M.W. State, Sequence variants in SLITRK1 are associated with Tourette's syndrome, Science 310 (5746) (2005) 317–320.
[2] L.N. Antar, J.B. Dictenberg, M. Plociniak, R. Afroz, G.J. Bassell, Localization of FMRP-associated mRNA granules and requirement of microtubules for activity-dependent trafficking in hippocampal neurons, Genes Brain Behav. 4 (6) (2005) 350–359.
[3] S.I. Ashraf, A.L. McLoon, S.M. Sclarsic, S. Kunes, Synaptic protein synthesis associated with memory is regulated by the RISC pathway in Drosophila, Cell 124 (1) (2006) 191–205.
[4] C.H. Bailey, E.R. Kandel, K. Si, The persistence of long-term memory: a molecular approach to self-sustaining changes in learning-induced synaptic growth, Neuron 44 (1) (2004) 49–57.
[5] S. Barik, An intronic microRNA silences genes that are functionally antagonistic to its host gene, Nucleic Acids Res. 36 (16) (2008) 5232–5241.
[6] D.P. Bartel, microRNAs: genomics, biogenesis, mechanism, and function, Cell 116 (2) (2004) 281–297.
[7] S.N. Bhattacharyya, R. Habermacher, U. Martine, E.I. Closs, W. Filipowicz, Relief of microRNA-mediated translational repression in human cells subjected to stress, Cell 125 (6) (2006) 1111–1124.
[8] G.M. Borchert, W. Lanier, B.L. Davidson, RNA polymerase III transcribes human microRNAs, Nat. Struct. Mol. Biol. 13 (12) (2006) 1097–1101.
[9] N. Bushati, S.M. Cohen, microRNA functions, Annu. Rev. Cell Dev. Biol. 23 (2007) 175–205.
[10] I. Bussing, F.J. Slack, H. Grosshans, let-7 microRNAs in development, stem cells and cancer, Trends Mol. Med. 14 (9) (2008) 400–409.
[11] X. Cao, S.L. Pfaff, F.H. Gage, A functional study of miR-124 in the developing neural tube, Genes Dev. 21 (5) (2007) 531–536.
[12] A.A. Caudy, M. Myers, G.J. Hannon, S.M. Hammond, Fragile X-related protein and VIG associate with the RNA interference machinery, Genes Dev. 16 (19) (2002) 2491–2496.
[13] H.Y. Cheng, J.W. Papp, O. Varlamova, H. Dziema, B. Russell, J.P. Curfman, T. Nakazawa, K. Shimizu, H. Okamura, S. Impey, K. Obrietan, microRNA modulation of circadian-clock period and entrainment, Neuron 54 (5) (2007) 813–829.
[14] P.S. Choi, L. Zakhary, W.Y. Choi, S. Caron, E. Alvarez-Saavedra, E.A. Miska, M. McManus, B. Harfe, A.J. Giraldez, H.R. Horvitz, A.F. Schier, C. Dulac, Members of the miRNA-200 family regulate olfactory neurogenesis, Neuron 57 (1) (2008) 41–55.
[15] B.R. Cullen, Transcription and processing of human microRNA precursors, Mol. Cell 16 (6) (2004) 861–865.

[16] T.H. Davis, T.L. Cuellar, S.M. Koch, A.J. Barker, B.D. Harfe, M.T. McManus, E.M. Ullian, Conditional loss of Dicer disrupts cellular and tissue morphogenesis in the cortex and hippocampus, J. Neurosci. 28 (17) (2008) 4322–4330.
[17] D. De Pietri Tonelli, J.N. Pulvers, C. Haffner, E.P. Murchison, G.J. Hannon, W.B. Huttner, miRNAs are essential for survival and differentiation of newborn neurons but not for expansion of neural progenitors during early neurogenesis in the mouse embryonic neocortex, Development 135 (23) (2008) 3911–3921.
[18] J. Dostie, Z. Mourelatos, M. Yang, A. Sharma, G. Dreyfuss, Numerous microRNPs in neuronal cells containing novel microRNAs, RNA 9 (2) (2003) 180–186.
[19] Y. Feng, C.A. Gutekunst, D.E. Eberhart, H. Yi, S.T. Warren, S.M. Hersch, Fragile X mental retardation protein: nucleocytoplasmic shuttling and association with somatodendritic ribosomes, J. Neurosci. 17 (5) (1997) 1539–1547.
[20] R. Fiore, S. Khudayberdiev, M. Christensen, G. Siegel, S. Flavell, T.K. Kim, M.E. Greenberg, G. Schratt, Mef2-mediated transcription of the miR379-410 cluster regulates activity-dependent dendritogenesis by fine-tuning Pumilio2 protein levels, EMBO J. 28 (6) (2009) 697–710.
[21] S.W. Flavell, M.E. Greenberg, Signaling mechanisms linking neuronal activity to gene expression and plasticity of the nervous system, Annu. Rev. Neurosci. 31 (2008) 563–590.
[22] A.J. Giraldez, R.M. Cinalli, M.E. Glasner, A.J. Enright, J.M. Thomson, S. Baskerville, S.M. Hammond, D.P. Bartel, A.F. Schier, microRNAs regulate brain morphogenesis in zebrafish, Science 308 (5723) (2005) 833–838.
[23] S. Griffiths-Jones, The microRNA Registry, Nucleic Acids Res. 32 (Database issue) (2004) D109–D111.
[24] S.S. Hebert, K. Horre, L. Nicolai, B. Bergmans, A.S. Papadopoulou, A. Delacourte, B. De Strooper, microRNA regulation of Alzheimer's amyloid precursor protein expression, Neurobiol. Dis. 33 (3) (2008) 422–428.
[25] S.S. Hebert, K. Horre, L. Nicolai, A.S. Papadopoulou, W. Mandemakers, A.N. Silahtaroglu, S. Kauppinen, A. Delacourte, B. De Strooper, Loss of microRNA cluster miR-29a/b-1 in sporadic Alzheimer's disease correlates with increased BACE1/beta-secretase expression, Proc. Natl. Acad. Sci. U.S.A. 105 (17) (2008) 6415–6420.
[26] I. Heo, C. Joo, J. Cho, M. Ha, J. Han, V.N. Kim, Lin28 mediates the terminal uridylation of let-7 precursor microRNA, Mol. Cell 32 (2) (2008) 276–284.
[27] P. Jin, D.C. Zarnescu, S. Ceman, M. Nakamoto, J. Mowrey, T.A. Jongens, D.L. Nelson, K. Moses, S.T. Warren, Biochemical and genetic interaction between the fragile X mental retardation protein and the microRNA pathway, Nat. Neurosci. 7 (2) (2004) 113–117.
[28] J.S. Karres, V. Hilgers, I. Carrera, J. Treisman, S.M. Cohen, The conserved microRNA miR-8 tunes atrophin levels to prevent neurodegeneration in Drosophila, Cell 131 (1) (2007) 136–145.
[29] J. Kim, K. Inoue, J. Ishii, W.B. Vanti, S.V. Voronov, E. Murchison, G. Hannon, A. Abeliovich, A microRNA feedback circuit in midbrain dopamine neurons, Science 317 (5842) (2007) 1220–1224.
[30] M.E. Klein, D.T. Lioy, L. Ma, S. Impey, G. Mandel, R.H. Goodman, Homeostatic regulation of MeCP2 expression by a CREB-induced microRNA, Nat. Neurosci. 10 (12) (2007) 1513–1514.
[31] W.P. Kloosterman, R.H. Plasterk, The diverse functions of microRNAs in animal development and disease, Dev. Cell 11 (4) (2006) 441–450.
[32] J. Kocerha, M.A. Faghihi, M.A. Lopez-Toledano, J. Huang, A.J. Ramsey, M.G. Caron, N. Sales, D. Willoughby, J. Elmen, H.F. Hansen, H. Orum, S. Kauppinen, P.J. Kenny, C. Wahlestedt, microRNA-219 modulates NMDA receptor-mediated neurobehavioral dysfunction, Proc. Natl. Acad. Sci. U.S.A. 106 (9) (2009) 3507–3512.
[33] A. Krek, D. Grun, M.N. Poy, R. Wolf, L. Rosenberg, E.J. Epstein, P. MacMenamin, I. da Piedade, K.C. Gunsalus, M. Stoffel, N. Rajewsky, Combinatorial microRNA target predictions, Nat. Genet. 37 (5) (2005) 495–500.
[34] A.M. Krichevsky, K.S. King, C.P. Donahue, K. Khrapko, K.S. Kosik, A microRNA array reveals extensive regulation of microRNAs during brain development, RNA 9 (10) (2003) 1274–1281.
[35] A.M. Krichevsky, K.C. Sonntag, O. Isacson, K.S. Kosik, Specific microRNAs modulate embryonic stem cell-derived neurogenesis, Stem Cells 24 (4) (2006) 857–864.
[36] M. Lagos-Quintana, R. Rauhut, A. Yalcin, J. Meyer, W. Lendeckel, T. Tuschl, Identification of tissue-specific microRNAs from mouse, Curr. Biol. 12 (9) (2002) 735–739.
[37] C. Leucht, C. Stigloher, A. Wizenmann, R. Klafke, A. Folchert, L. Bally-Cuif, microRNA-9 directs late organizer activity of the midbrain-hindbrain boundary, Nat. Neurosci. 11 (6) (2008) 641–648.
[38] B.P. Lewis, C.B. Burge, D.P. Bartel, Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets, Cell 120 (1) (2005) 15–20.
[39] Y. Li, L. Lin, P. Jin, The microRNA pathway and fragile X mental retardation protein, Biochim. Biophys. Acta 1779 (11) (2008) 702–705.
[40] Z. Li, Y. Zhang, L. Ku, K.D. Wilkinson, S.T. Warren, Y. Feng, The fragile X mental retardation protein inhibits translation via interacting with mRNA, Nucleic Acids Res. 29 (11) (2001) 2276–2283.
[41] L.P. Lim, N.C. Lau, P. Garrett-Engele, A. Grimson, J.M. Schelter, J. Castle, D.P. Bartel, P.S. Linsley, J.M. Johnson, Microarray analysis shows that some microRNAs downregulate large numbers of target mRNAs, Nature 433 (7027) (2005) 769–773.
[42] G. Lugli, J. Larson, M.E. Martone, Y. Jones, N.R. Smalheiser, Dicer and eIF2c are enriched at postsynaptic densities in adult mouse brain and are modified by neuronal activity in a calpain-dependent manner, J. Neurochem. 94 (4) (2005) 896–905.
[43] G. Lugli, V.I. Torvik, J. Larson, N.R. Smalheiser, Expression of microRNAs and their precursors in synaptic fractions of adult mouse forebrain, J. Neurochem. 106 (2) (2008) 650–661.
[44] E.V. Makeyev, J. Zhang, M.A. Carrasco, T. Maniatis, The microRNA miR-124 promotes neuronal differentiation by triggering brain-specific alternative pre-mRNA splicing, Mol. Cell 27 (3) (2007) 435–448.
[45] B.R. Maller Schulman, X. Liang, C. Stahlhut, C. DelConte, G. Stefani, F.J. Slack, The let-7 microRNA target gene, Mlin41/Trim71 is required for mouse embryonic survival and neural tube closure, Cell Cycle 7 (24) (2008) 3935–3942.
[46] E.A. Miska, E. Alvarez-Saavedra, M. Townsend, A. Yoshii, N. Sestan, P. Rakic, M. Constantine-Paton, H.R. Horvitz, Microarray analysis of microRNA expression in the developing mammalian brain, Genome Biol. 5 (9) (2004) R68.
[47] M.A. Newman, J.M. Thomson, S.M. Hammond, Lin-28 interaction with the Let-7 precursor loop mediates regulated microRNA processing, RNA 14 (8) (2008) 1539–1549.
[48] E.A. Nimchinsky, A.M. Oberlander, K. Svoboda, Abnormal development of dendritic spines in FMR1 knock-out mice, J. Neurosci. 21 (14) (2001) 5139–5146.
[49] K. Okamura, A. Ishizuka, H. Siomi, M.C. Siomi, Distinct roles for Argonaute proteins in small RNA-directed RNA cleavage pathways, Genes Dev. 18 (14) (2004) 1655–1666.
[50] A.N. Packer, Y. Xing, S.Q. Harper, L. Jones, B.L. Davidson, The bifunctional microRNA miR-9/miR-9* regulates REST and CoREST and is downregulated in Huntington's disease, J. Neurosci. 28 (53) (2008) 14341–14346.
[51] R.S. Pillai, S.N. Bhattacharyya, W. Filipowicz, Repression of protein synthesis by miRNAs: how many mechanisms? Trends Cell Biol. 17 (3) (2007) 118–126.
[52] S. Roush, F.J. Slack, The let-7 family of microRNAs, Trends Cell Biol. 18 (10) (2008) 505–516.
[53] A. Rybak, H. Fuchs, L. Smirnova, C. Brandt, E.E. Pohl, R. Nitsch, F.G. Wulczyn, A feedback loop comprising lin-28 and let-7 controls pre-let-7 maturation during neural stem-cell commitment, Nat. Cell Biol. 10 (8) (2008) 987–993.
[54] A. Schaefer, D. O'Carroll, C.L. Tan, D. Hillman, M. Sugimori, R. Llinas, P. Greengard, Cerebellar neurodegeneration in the absence of microRNAs, J. Exp. Med. 204 (7) (2007) 1553–1558.
[55] G.M. Schratt, F. Tuebing, E.A. Nigh, C.G. Kane, M.E. Sabatini, M. Kiebler, M.E. Greenberg, A brain-specific microRNA regulates dendritic spine development, Nature 439 (7074) (2006) 283–289.
[56] M. Shibata, D. Kurokawa, H. Nakao, T. Ohmura, S. Aizawa, microRNA-9 modulates Cajal-Retzius cell differentiation by suppressing Foxg1 expression in mouse medial pallium, J. Neurosci. 28 (41) (2008) 10415–10421.
[57] G. Siegel, G. Obernosterer, R. Fiore, M. Oehmen, S. Bicker, M. Christensen, S. Khudayberdiev, P.F. Leuschner, C.J.L. Busch, C. Kane, K. Hübel, F. Dekker, C. Hedberg, B. Rengarajan, C. Drepper, H. Waldmann, S. Kauppinen, M.E. Greenberg, A. Draguhn, M. Rehmsmeier, J. Martinez, G.M. Schratt, A functional screen implicates microRNA-138-dependent regulation of the depalmitoylation enzyme APT1 in dendritic spine morphogenesis, Nat. Cell Biol., in press.
[58] F.J. Slack, M. Basson, Z. Liu, V. Ambros, H.R. Horvitz, G. Ruvkun, The lin-41 RBCC gene acts in the *C. elegans* heterochronic pathway between the let-7 regulatory RNA and the LIN-29 transcription factor, Mol. Cell 5 (4) (2000) 659–669.
[59] L. Smirnova, A. Grafe, A. Seiler, S. Schumacher, R. Nitsch, F.G. Wulczyn, Regulation of miRNA expression during neural cell specification, Eur. J. Neurosci. 21 (6) (2005) 1469–1477.
[60] K.L. Stark, B. Xu, A. Bagchi, W.S. Lai, H. Liu, R. Hsu, X. Wan, P. Pavlidis, A.A. Mills, M. Karayiorgou, J.A. Gogos, Altered brain microRNA biogenesis contributes to phenotypic deficits in a 22q11-deletion mouse model, Nat. Genet. 40 (6) (2008) 751–760.
[61] M.A. Sutton, E.M. Schuman, Dendritic protein synthesis, synaptic plasticity, and memory, Cell 127 (1) (2006) 49–58.
[62] R. Vassar, B.D. Bennett, S. Babu-Khan, S. Kahn, E.A. Mendiaz, P. Denis, D.B. Teplow, S. Ross, P. Amarante, R. Loeloff, Y. Luo, S. Fisher, J. Fuller, S. Edenson, J. Lile, M.A. Jarosinski, A.L. Biere, E. Curran, T. Burgess, J.C. Louis, F. Collins, J. Treanor, G. Rogers, M. Citron, Beta-secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE, Science 286 (5440) (1999) 735–741.
[63] M.C. Vella, E.Y. Choi, S.Y. Lin, K. Reinert, F.J. Slack, The *C. elegans* microRNA let-7 binds to imperfect let-7 complementary sites from the lin-41 3′UTR, Genes Dev. 18 (2) (2004) 132–137.
[64] J. Visvanathan, S. Lee, B. Lee, J.W. Lee, S.K. Lee, The microRNA miR-124 antagonizes the anti-neural REST/SCP1 pathway during embryonic CNS development, Genes Dev. 21 (7) (2007) 744–749.
[65] S.R. Viswanathan, G.Q. Daley, R.I. Gregory, Selective blockade of microRNA processing by Lin28, Science 320 (5872) (2008) 97–100.
[66] N. Vo, M.E. Klein, O. Varlamova, D.M. Keller, T. Yamamoto, R.H. Goodman, S. Impey, A cAMP-response element binding protein-induced microRNA regulates neuronal morphogenesis, Proc. Natl. Acad. Sci. U.S.A. 102 (45) (2005) 16426–16431.
[67] G. Wang, J.M. van der Walt, G. Mayhew, Y.J. Li, S. Zuchner, W.K. Scott, E.R. Martin, J.M. Vance, Variation in the miRNA-433 binding site of FGF20 confers risk for Parkinson disease by overexpression of alpha-synuclein, Am. J. Hum. Genet. 82 (2) (2008) 283–289.
[68] W.X. Wang, B.W. Rajeev, A.J. Stromberg, N. Ren, G. Tang, Q. Huang, I. Rigoutsos, P.T. Nelson, The expression of microRNA miR-107 decreases early in Alzheimer's disease and may accelerate disease progression through regulation of beta-site amyloid precursor protein-cleaving enzyme 1, J. Neurosci. 28 (5) (2008) 1213–1223.

[69] G.A. Wayman, M. Davare, H. Ando, D. Fortin, O. Varlamova, H.Y. Cheng, D. Marks, K. Obrietan, T.R. Soderling, R.H. Goodman, S. Impey, An activity-regulated microRNA controls dendritic plasticity by down-regulating p250GAP, Proc. Natl. Acad. Sci. U.S.A. 105 (26) (2008) 9093–9098.
[70] I.J. Weiler, C.C. Spangler, A.Y. Klintsova, A.W. Grossman, S.H. Kim, V. Bertaina-Anglade, H. Khaliq, F.E. de Vries, F.A. Lambers, F. Hatia, C.K. Base, W.T. Greenough, Fragile X mental retardation protein is necessary for neurotransmitter-activated protein translation at synapses, Proc. Natl. Acad. Sci. U.S.A. 101 (50) (2004) 17504–17509.
[71] E. Wienholds, W.P. Kloosterman, E. Miska, E. Alvarez-Saavedra, E. Berezikov, E. de Bruijn, H.R. Horvitz, S. Kauppinen, R.H. Plasterk, microRNA expression in zebrafish embryonic development, Science 309 (5732) (2005) 310–311.
[72] L. Wu, J.G. Belasco, Micro-RNA regulation of the mammalian lin-28 gene during neuronal differentiation of embryonal carcinoma cells, Mol. Cell Biol. 25 (21) (2005) 9198–9208.
[73] F.G. Wulczyn, L. Smirnova, A. Rybak, C. Brandt, E. Kwidzinski, O. Ninnemann, M. Strehle, A. Seiler, S. Schumacher, R. Nitsch, Post-transcriptional regulation of the let-7 microRNA during neural cell specification, FASEB J. 21 (2) (2007) 415–426.
[74] X.L. Xu, Y. Li, F. Wang, F.B. Gao, The steady-state level of the nervous-system-specific microRNA-124a is regulated by dFMR1 in Drosophila, J. Neurosci. 28 (46) (2008) 11883–11889.
[75] J. Yu, M.A. Vodyanik, K. Smuga-Otto, J. Antosiewicz-Bourget, J.L. Frane, S. Tian, J. Nie, G.A. Jonsdottir, V. Ruotti, R. Stewart, I.I. Slukvin, J.A. Thomson, Induced pluripotent stem cell lines derived from human somatic cells, Science 318 (5858) (2007) 1917–1920.
[76] J.Y. Yu, K.H. Chung, M. Deo, R.C. Thompson, D.L. Turner, microRNA miR-124 regulates neurite outgrowth during neuronal differentiation, Exp. Cell Res. 314 (14) (2008) 2618–2633.
[77] Y. Zhao, D. Srivastava, A developmental view of microRNA function, Trends Biochem. Sci. 32 (4) (2007) 189–197.