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MicroRNAs of the miR379–410 cluster: New players in embryonic neurogenesis and regulators of neuronal function

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The imprinted miR379–410 cluster contains 38 microRNAs (miRNAs) that are involved in diverse neurodevelopmental processes and are important regulators of neuronal function. The implications of these miRNAs in neurological diseases have been recently recognized.In the present minireview, the current findings regarding the brain-specific functions of miR379–410 cluster miRNAs are summarized and discussed.

Introduction

MicroRNAs (miRNAs) are small, ~22-nucleotide noncoding RNAs, which bind to sequences located mainly in the 3′-untranslated regions (3′UTRs) of their target transcripts. Upon miRNA binding, the respective target mRNAs are generally either degraded or blocked in their translation (summarized in[1,2]). Recent studies have implicated miRNAs in various aspects of neuronal development and function. During development, miRNAs regulate neural induction, neural stem cell expansion, neuronal differentiation and subtype specification as well as neuronal migration. Furthermore, miRNAs are critically involved in regulating neuritogenesis, neuronal function and synaptic plasticity (summarized in[3,4]). The first experiments that demonstrated the essential roles of miRNAs during neuronal development were based upon ablation of components of the miRNA processing machinery, i.e. Dicer or DGCR8. Since then, neural functions of single miRNAs have been identified in a number of studies. Nevertheless, many more miRNAs are expressed in the developing and/or mature brain and the functions of the majority of these brain-expressed miRNAs are still unknown.

The miR379–410 cluster is a large genomic miRNA cluster with brain-specific functions. It is located on chromosome 14 in humans and 12 in mice and is exclusively expressed from the maternal allele. It contains 38 brain-expressed miRNAs, only few of which have so far been studied concerning their brain-specific functions. This limited number of studies indicates that miR379–410 cluster miRNAs are involved in various aspects of neurodevelopment, neuronal maturation and function and that their mis-regulation might contribute to the development of neurological and neuropsychiatric diseases. In this review I will summarize the current knowledge about the miR379–410 cluster miRNA expression in the brain, its role in neurodevelopment and neuronal function and its involvement in neurological diseases (**Table 1**).

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The miR379–410 Cluster is Located Within the DLK1-DIO3 Imprinted Region

The miR379–410 cluster is located within the *DLK1-DIO3* imprinted region which is situated on chromosome 14q32 in humans and on the distal part of chromosome 12 (12qF1) in mice (summarized in[5]; **Fig. 1**). In 1993 Cattanach and Rasberry provided the first evidence that genomic imprinting at this locus is important.[6] They generated mice with either maternal or paternal uniparental disomy (upd) of the whole chromosome 12 or only of its distal part (Mat(Di)12; MatDp(dist12) or Pat(Di)12; PatDp(dist12)). Mat(Di)12, MatDp(dist12), Pat(Di)12 and PatDp(dist12) mice were prenatally lethal and exhibited severe developmental defects (see below and summarized in[5]). Since these groundbreaking experiments, a growing number of human patients have been reported with maternal or paternal upd of human chromosome 14. In humans both paternal and maternal upd for chromosome 14 (upd(14)pat and upd(14)mat) cause distinct phenotypes. Upd(14)pat (OMIM 608149) causes a severe phenotype that includes skeletal abnormalities such as a bell-shaped thorax, facial dysmorphisms and developmental delay/intellectual disability (ID). Upd(14)mat leads to a milder phenotype than upd(14)pat including short stature, hypotonia, mild facial abnormalities, precocious onset of puberty and mild developmental delay.[7,8] In the mouse, upd for chromosome 12 also results in distinct phenotypes that partially overlap with those in human upd(14). Thus, paternal upd for chromosome 12 [PatDi(12)] leads to prenatal lethality, abdominal distension, skeletal defects, cardiac abnormalities

Table 1. Functions and targets of miR379–410 cluster miRNAs

Mir379–410 cluster miRNA	Brain targets	Brain-specific function	Involvement in brain disorders	Reference
miR-134	Pum2, Chrdl-1, Dcx, Limk1, CREB	Promotes NPC proliferation, inhibits neuron migration, sensitizes neurons to BMP-induced neurite outgrowth, activity-induced, promotes activity-induced dendritogenesis, inhibits spine growth and density	Silencing miR-134 is neuroprotective in a mouse epilepsy model; downregulated in PBMCs from schizophrenia patients; upregulated in dorsolateral PFC Brodmann area 46 in schizophrenia	25,28,29,46,50-52
miR-154	—	—	Downregulated in PBMCs from schizophrenia patients, Upregulated in cerebellum in Mecp2 KO mice, downregulated in glioma	52,54,57
miR-299	—	—	Upregulated in cerebellum in Mecp2 KO mice, downregulated in glioma	54,57
miR-300	—	—	Upregulated in cerebellum in Mecp2 KO mice	54
miR-323–3p	—	—	Downregulated in PBMCs from schizophrenia patients, Upregulated in cerebellum in Mecp2 KO mice, downregulated in glioma	52,54,57
miR-329	—	Activity-induced, promotes activity-induced dendritogenesis	Downregulated in PBMCs from schizophrenia patients	28,52
miR-369–3p	N-cadherin	Promotes neuronal differentiation, inhibits neuronal migration	Upregulated in cerebellum in Mecp2 KO mice, downregulated in glioma	21,54,57
miR-376a	Hes5	Promotes neuronal differentiation	Upregulated in lymphoblastoid cell lines from ASD patients, downregulated in glioma	30,53,57
miR-377	—	—	Upregulated in cerebellum in Mecp2 KO mice	54
miR-380	—	—	Upregulated in cerebellum in Mecp2 KO mice	54
miR-381	—	Activity-induced, promotes activity-induced dendritogenesis	Upregulated in cerebellum in Mecp2 KO mice, downregulated in glioma	28,54,57
miR-382	—	—	Upregulated in cerebellum in Mecp2 KO mice	54
miR-409–3p	—	—	Downregulated in PBMCs from schizophrenia patients	52
miR-410	—	—	Downregulated in PBMCs from schizophrenia patients, upregulated in cerebellum in Mecp2 KO mice	52,54
miR-485	SV2A	Activity-induced, inhibits spine density and maturation, inhibits spontaneous synaptic activity	Downregulated in PBMCs from schizophrenia patients	25,26,52
miR-487b	—	—	Downregulated in PBMCs from schizophrenia patients, upregulated in glioblastoma	52,56
miR-495	—	Activity-induced	Downregulated in lymphoblastoid cell lines from ASD patients, upregulated in cerebellum in Mecp2 KO mice	28,53,54
miR-496	N-cadherin	Promotes neuronal differentiation, inhibits neuronal migration		21
miR-541	—	Activity-induced		28
miR-543	N-cadherin	Promotes neuronal differentiation, inhibits neuronal migration	Upregulated in cerebellum in Mecp2 KO mice, downregulated in glioblastoma	21,54,56
miR-544	—	—	Downregulated in PBMCs from schizophrenia patients, upregulated in cerebellum in Mecp2 KO mice	52,54
miR-654–5p	—	—	Downregulated in PBMCs from schizophrenia patients	52

and placentomegaly. [MatDi(12)] causes a phenotype that includes perinatal lethality, growth failure and placental hypoplasia.[9,10]

In the years following the discovery of genomic imprinting on mouse chromosome 12 and human chromosome 14 the imprinted region which was later named *DLK1-DIO3* region was characterized and it was shown that it contains several coding and non-coding genes (summarized in[5]).

The *DLK1-DIO3* region spans ~850 kb and contains the paternally expressed genes *DLK1*, *RTL1* and *DIO3* and maternally expressed genes *MEG3* (*Gtl2* in mice), *MEG8* (*RIAN* in mice) and antisense *RTL1* (RTL1as). DLK1 acts as an antagonist of Notch signaling and regulates cell differentiation.[11,12] RTL1 is a retrotransposon-like gene expressed in a subset of embryonic tissues as well as in the placenta and is essential for proper placental development.[13,14] DIO3 is a type 3-iodothyronine

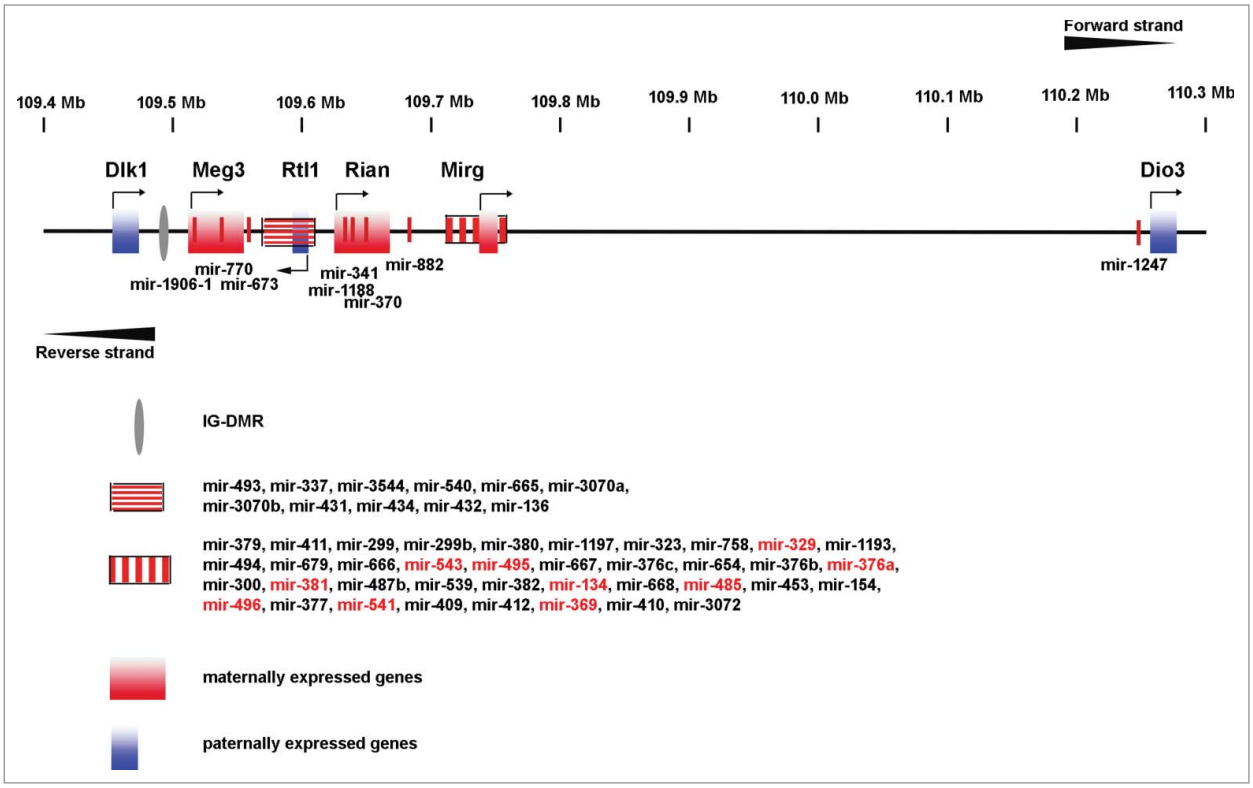

Figure 1. Schematic overview of the *DLK1-DIO3* genomic region on mouse chromosome 12 (GRCm38/mm10 Assembly). Genes, long noncoding RNAs and miRNAs are noted. MiR379–410 cluster miRNAs that have been subject to functional studies in the brain are depicted in red color. Pseudogenes and snoRNAs are not shown.

deiodinase, which degrades thyroid hormone.[15,16] Both MEG3 and MEG8 are noncoding RNAs.

Imprinting in this region is controlled by 2 distinct, differentially methylated regions (DMR): a primary, germline-derived *DLK1-MEG3* intergenic DMR (IG-DMR) and a secondary, post-fertilization-derived *MEG3*-DMR. Both DMRs are hypermethylated on the paternal allele and hypomethylated on the maternal allele (summarized in[5]).

The *DLK1-DIO3* imprinted region also contains 53 miRNAs on the forward strand and one miRNA on the reverse strand. Most of these miRNAs were discovered by a computer-assisted approach in 2004.[17,18] The 54 miRNAs are separated into 3 different clusters with miR-2392 and miR-770 being situated in the *DLK1-MEG3* region, the second cluster between *MEG3* and *MEG8* and the third (the miR379–410 cluster) between *MEG8* and *DIO3*.

Because miRNAs of the region are exclusively expressed from the maternal allele they are expected to be upregulated in patients with upd(14)mat and downregulated in patients with upd(14)pat as is the case for mouse [MatDi(12)] and [PatDi(12)]. In line with growing evidence that miRNAs of the miR379–410 cluster are essential regulators of neurogenesis and neuron function it seems likely that such a mis-expression of these miRNAs contributes to the development of an ID, which is seen in patients with upd(14)pat. Identified deletions in humans encompassing parts of the *DLK1-DIO3* region support this hypothesis. Thus, maternal inheritance of these deletions fully phenocopied the upd(14)pat phenotype although *DLK1* levels were normal. This finding suggests that the upd(14)pat phenotype (including the ID) might be caused by a loss of maternally expressed noncoding RNAs.[5] However, the early lethality that occurs in the mouse models has precluded the analyses of possible impairments in brain function that might be caused by altered miRNA expression.[9] A recently generated knockout mouse model may clarify this issue.[19]

The miRNAs of the miR379–410 cluster are highly conserved between human and mouse. Most of the pre-miRNAs of the cluster are arranged in tandem arrays of closely related sequences resulting from genomic duplications.[20] Unlike the pre-miRNAs the mature sequences show a high diversity and predicted miRNA target genes as well. Because of the broad spectrum of predicted targets and the specific expression patterns of miR379–410 cluster miRNAs it has been suggested that these miRNAs might target numerous genes in specific cell types.[20] In addition, we have shown recently that numerous miRNAs of the cluster target the same gene, *N-cadherin*, in an additive manner in the developing mouse neocortex.[21]

The regulation of expression of the genes and miRNAs located in the *DLK1-DIO3* region is poorly studied. It is hypothesized but not yet proven that the maternally expressed genes and miRNAs of the *DLK1-DIO3* region are transcribed as one giant polycistronic transcript from which individual genes and miRNAs are

derived by posttranscriptional processing.[22] However, this may be an oversimplification. While the genes and the few miRNAs of the region that have been studied share similar expression domains in the developing and mature brain, differences in expression do exist. *Gtl2*, for example, is not only expressed during development but also in the adult brain, whereas expression of miR-410 is restricted to developmental and early postnatal stages.[23,24] In contrast, expression of 2 other miRNAs of the region, miR-134 and miR-485, increases postnatally.[25,26] More evidence exists that, besides a giant polycistronic transcript, expression of the genes and miRNAs of the region may be driven by gene-specific transcriptional mechanisms. Thus, 7 independently maternally expressed noncoding RNA genes including *Gtl2* and *Mirg* have recently been identified in the region on mouse chromosome 12qF1.[27] Moreover, it has been shown that several miRNAs of the miR379–410 cluster but not *Gtl2* undergo an activity-induced upregulation in their expression which is driven by the binding of Mef2 to a binding site ~20 kb upstream of the miR379–410 cluster.[26,28] During embryonic neocortex development miR-134 is poorly expressed in neural progenitors but is upregulated in postmitotic neurons, whereas 3 other miRNAs of the cluster, miR-369–3p, -496 and -543 are expressed in neural progenitors and neurons.[21,25] MiR-134 as well as miR-369 and miR-496 are encoded within exons or introns of the noncoding RNA gene *Mirg* in the mouse and are therefore likely co-regulated at the transcriptional level. Expression differences may therefore be due to posttranscriptional regulation, which should be studied in the future.

miRNAs of the miR379–410 Cluster Regulate Neurogenesis and Neuronal Migration in the Mouse Embryo

Brain-enriched miRNAs are involved in all aspects of neurogenesis and fine-tune the expression of those genes that control proliferation and differentiation of neural progenitor cells (NPCs). While some miRNAs, e.g. miR-9, miR-124 and let-7, promote neuronal differentiation, others, such as miR-184, maintain NPCs in a proliferating state. In addition, brain-enriched miRNAs regulate neuronal migration (e.g.,[21,29]). Several studies have shown that miRNAs of the miR379–410 cluster are involved in all these processes.

The Notch pathway controls NPC expansion and cell fate specifications in the developing brain. Pathway activation maintains NPCs in a proliferating state whereas its downregulation promotes neuronal differentiation. Several components of the Notch pathway are subject to miRNA-dependent regulation, which may be important to balance Notch signaling in NPCs (summarized in[3]). MiR-124 targets the Notch ligand Jag1 and the Notch effector Sox9. MiR-9 targets several members of the Hes family of transcription factors in zebrafish and murine NPCs, thereby controlling the timing of NPC differentiation. A member of the miR379–410 cluster, miR-376a, targets Hes5 mRNA and positively regulates neuronal differentiation of cultured rat cortical stem cells.[30] Although an interesting finding, it remains to be analyzed if such a regulation of Hes5 by miR376a occurs *in vivo* and is necessary for driving neurogenesis in the embryonic CNS.

Whereas miR-376a promotes neural differentiation another miRNA of the cluster, miR-541, targets synapsin I and inhibits neurite formation and neuronal differentiation when overexpressed in PC12 cells.[31] However, as for miR376a, there is presently a lack of *in vivo* evidence.

Recent studies have indicated that miRNAs of the miR379–410 cluster are important regulators of neurogenesis and neuronal migration in the developing neocortex *in vivo* where they have both overlapping and antagonistic functions. As outlined above, miR-134 is poorly expressed in neural progenitors and is upregulated in postmitotic neurons. When overexpressed in neural progenitors, however, miR-134 promotes cell proliferation *in vitro* and in *vivo*. In postmitotic neurons, miR-134 negatively regulates their migration into the cortical plate by targeting Chordin-like 1 (Chrdl-1) and Doublecortin (Dcx) and sensitizes neurons to BMP-induced neurite outgrowth.[29] The regulation of Dcx by miR-134 is an interesting finding as Dcx is an important effector of the Reelin pathway and controls neuronal migration. Mutations in Reelin pathway genes, e.g. the *RELN*, *DCX* or *LIS1* genes, cause a neuronal migration disorder, lissencephaly, in humans. An abnormal reduction of *RELN* has also been observed in schizophrenia and autism (summarized in[32]). The Reelin pathway is fine-tuned by the action of several miRNAs that inhibit neuronal migration. Beside miR-134, other miRNAs that are not encoded within the miR379–410 cluster have been implicated in Reelin pathway regulation. Recent studies carried out in chicken hypothalamic cells and neuroblastoma cells suggest that miR-138 and miR-128 target reelin and miR-128 DCX in addition.[33,34] MiR-139–5p inhibits cell migration *in vitro* and modulates rat brain development by targeting Lis1.[35] MiR-22 and miR-124 target components of the CoREST/REST transcriptional repressor complex in the cortical wall, thereby regulating Dcx indirectly in migrating neurons.[36] A mechanism involving miRNAs may explain reduced expression of Reelin pathway components in neurodevelopmental disorders and should be explored in the future.

As outlined above, miR-134 has stage-specific effects on embryonic cortical development. Also other miRNAs of the miR379–410 cluster have these stage-specific effects. We have recently found that 3 members of the cluster, miR-369–3p, -496 and -543, are expressed in NPCs and in neurons. These miRNAs target the mRNA encoding the cell adhesion protein N-cadherin in an additive manner.[21] N-cadherin is widely expressed in the developing neocortex in neural progenitor cells and in neurons and has multiple functions. In the ventricular zone of the neocortex N-cadherin is an integral part of the adherens junctions and is essential for maintaining the architecture of the neocortex.[37,38] In radial glia cells (RGCs), N-cadherin activates β-catenin signaling and enhances proliferation.[38,39] In migrating neurons, N-cadherin is required for the motility of the cells toward the cortical plate.[40,41] Although N-cadherin is widely expressed in the developing neocortex its expression levels have to be kept in a physiological range because both its under- as well as its

overexpression causes defects in neuronal differentiation and migration. We have shown that the miRNAs of the miR379–410 cluster fine-tune the expression of N-cadherin and thereby ensure proper neurogenesis and neuronal migration. In contrast to miR-134 but similar to other brain-enriched miRNAs such as miR-124, they attenuate radial glia cell proliferation and enhance differentiation. In migrating neurons, they overlap in their function with miR-134 and negatively regulate neuronal migration.[21] These results indicate that the miRNAs of the miR379–410 cluster not only differ in their expression patterns but also in their functions. Murine MiR-134 as well as miR-369–3p and miR-496 are encoded within exons or introns of the noncoding RNA *Mirg* and therefore likely share the same transcriptional regulation. Differences in expression of these miRNAs may thus be due to specific posttranscriptional mechanisms.

miRNAs of the miR379–410 Cluster Control Neuronal Function

Neuronal activity regulates the expression of numerous brain-enriched miRNAs, with important consequences for neuronal homeostasis. Whereas some miRNAs such as the CREB-dependent miR-132 and miR-212 and all miR379–410 cluster miRNAs analyzed so far, are induced by neuronal activity others, e.g., miR-124, are decreased (summarized in[42]).

The activity-induced miR379–410 cluster miRNAs that have been analyzed so far, i.e., miR-134, -381, -329, -495, -541 and -485, control neuronal maturation and function.[26,28] For example, miR-485 targets the synaptic vesicle protein SV2A and negatively regulates spine density and maturation and reduces spontaneous synaptic activity, thereby controlling homeostatic synaptic plasticity.[26] Inhibition of miR-134, -381 or -329 but not of miR-495 or -541 blocks activity-induced dendritogenesis. The miRNA of the miR379–410 cluster which has been studied in most detail, miR-134, has apparently opposing effects by, at the same time, promoting activity-induced dendritogenesis and inhibiting spine growth by targeting Pum2 and Limk1, respectively. It has been suggested that these apparently opposing functions are indeed parts of the same homeostatic network that controls the overall neuronal excitability.[28] Both miR-134 and miR-485 localize to soma and dendrites in cultured hippocampal neurons and it is proposed that neuronal activity elevates miR-134 expression throughout the cell while concurrently inhibiting miR-134 locally in dendrites. Another possibility is that the upregulation of miR-134 expression upon neuronal stimulation is restricted to certain cell types. Indeed, several recent studies have shown that the activity-dependent increase of miR-134 is small in comparison to miR-132 and miR-212 and is restricted to parvalbumin, SST, glutamate decarboxylase 2 (GAD2) and Calretinin-positive interneurons. In contrast, miR-132 and miR-212 are predominantly expressed in Calcium/Calmodulin-dependent protein kinase II α (CamKIIα) positive glutamatergic neurons.[43-45]

Conflicting results exist concerning the regulation of spine density by miR-134. Thus the knockdown of miR-134 led to a reduction in spine density *in vivo*[46] but not *in vitro*.[25] The different experimental conditions used in the 2 studies might be causal for the observed differences.

It has been shown *in vivo* that miR-134 is a target of the transcription factor SIRT and controls long-term potentiation (LTP) and memory formation.[46,47] Brain-specific SIRT1 knockout mice show defects in LTP and cortical and hippocampal dependent memory. SIRT1 is a transcription factor that, together with YY1, represses miR-134 expression by binding to 2 sites that are located ~1 kb and 4 kb upstream of miR-134 in the genome.[47] In the SIRT1 knockout mice miR-134 is upregulated which leads to decreased protein levels of the miR-134 target CREB and consequently to a downregulation of the CREB target brain-derived neurotrophic factor (BDNF). *In vivo* miR-134 knockdown experiments using injections of LNA-miR-134 probes into hippocampal CA1 region of SIRT1 knockout mice restored LTP and partially restored memory impairments in these mice. In agreement with cell-type-specific functions for miR-134, miR-132 and miR-212 (see above) a miRNA microarray carried out with RNA from SIRT1 knockout hippocampi did not show an obvious decrease in expression of the CREB targets miR-132 or miR-212.

It is conceivable that the subcellular localization of a certain miRNA may influence its activity and may be important for the regulation of different sets of targets, thereby increasing the complexity of miRNA-mediated regulation in neurons. Whether other miRNAs of the miR379–410 cluster exhibit a specific subcellular localization or cell-type-specific expression is not known. Recent evidence has accumulated demonstrating that miRNA function is not restricted to the cytoplasm but that instead some miRNAs can re-enter the nucleus where they may be involved in posttranscriptional gene silencing of nuclear transcripts, transcriptional gene silencing and activation and regulation of alternative splicing. Similar to other cell types miRNAs have been detected in the nuclei of NPCs and neurons.[48,49] Whereas only a small fraction (5%) of neuron-expressed miRNAs is enriched in the nucleus the majority of miRNAs (including miR379–410 cluster miRNAs) seems to shuttle between the nucleus and cytoplasm in neurons. Future studies should aim at identifying possible nuclear functions of these miRNAs.

The Roles of miR379–410 Cluster miRNAs in Brain Disorders

In addition to their possible involvement in the upd(14)pat phenotype (see above) miRNAs of the miR379–410 cluster have been associated to neurodevelopmental disorders (i.e. epilepsy, schizophrenia and autism) and brain tumors (i.e., gliomas).

Silencing miR-134 has neuroprotective functions in a mouse epilepsy model. Status epilepticus (SE) results in elevated levels of mature miR-134 *in vitro* and *in vivo*.[46,50] Inhibition of miR-134 by injecting miR-134 specific antagomirs into the mouse ventricle prevented kainic acid (KA)-induced neurotoxicity in hippocampal neurons. Thus, silencing miR-134 reduced spontaneous recurrent seizures and altered pathologic hallmarks of

temporal lobe epilepsy, i.e. progressive neuron loss, gliosis and rearrangement of mossy fibers.

Altered levels of miR379–410 cluster miRNAs occur in human schizophrenia patients. Thus, several miRNAs of this cluster, including miR-134, miR-329, miR-409–3p, miR-487b, miR-544, miR-654–5p, miR-485–3p, miR-323–3p, miR-410 and miR-154, are significantly downregulated in peripheral blood mononuclear cells from schizophrenia patients.[51] The significance of their downregulation, however, is not clear. In the brain, 2 miRNAs of the cluster, miR-134 and miR-382, were found to be upregulated in the dorsolateral prefrontal cortex Brodmann area 46 in postmortem samples of schizophrenia patients.[52] In light of the known functions of miR379–410 cluster miRNAs during processes that are also affected in schizophrenia, e.g. the regulation of dendritic spine density, an altered expression of these miRNAs is of potential interest and may very well contribute to disease development. Additional studies are needed to functionally evaluate the role of miR379–410 cluster miRNAs in schizophrenia.

MiRNAs from the miR379–410 cluster were also reported to be differentially expressed between lymphoblastoid cell lines from autistic monozygotic twins and their unaffected sibling.[53] Further evidence for a possible involvement of miR379–410 cluster miRNAs in the etiology of autism spectrum disorders (ASD) comes from a study that analyzed changes in miRNA expression in methyl-CpG-binding protein 2 (Mecp2) knockout cerebella.[54] Mutations in the human *MECP2* gene cause Rett syndrome, an autism spectrum disorder with additional severe neurological symptoms, e.g., ataxia and seizures. MiR379–410 cluster miRNAs were constantly upregulated in the mouse knockout cerebella and were transcriptionally repressed by Mecp2. Again, functional studies are needed to shed light on the roles of these miRNAs in ASD.

Several studies have investigated the miRNA expression profiles in gliomas from human patients and the mouse and have found a downregulation of miR379–410 cluster miRNAs in comparison to normal brain tissue.[55-57] Lavon et al. have found that gliomas display a miRNA expression signature that is reminiscent of the profile of stem cells. Typical stem cell miRNAs such as the miR302–367 cluster miRNAs were upregulated in both gliomas and mouse NPCs. The miR379–410 cluster miRNAs were downregulated in both gliomas and normal mouse NPCs.[57] This suggests that miR379–410 cluster miRNAs may represent the largest tumor suppressor miRNA cluster in the genome. Further studies should aim at confirming the role of this cluster in glioma and test whether an increase in their expression may reduce tumorigenesis.

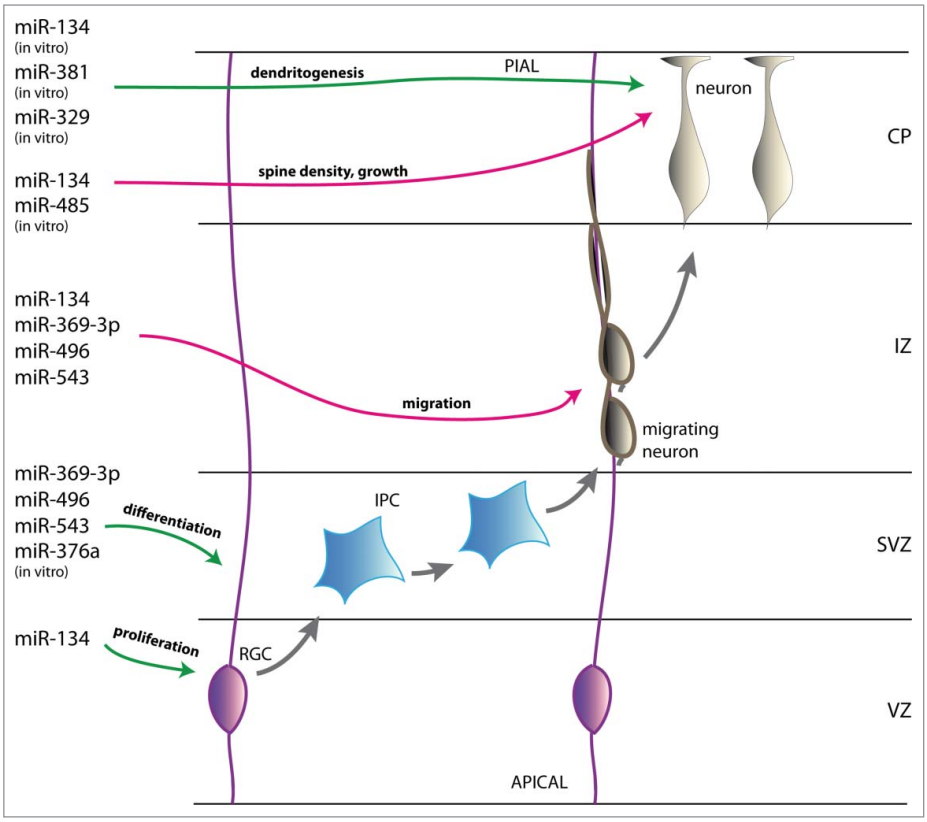

Figure 2. miR379–410 cluster miRNA regulation of cerebral cortex neurogenesis. Schematic representation of the developing cortical wall. During embryonic development of the cerebral cortex radial glial cells (RGCs, pink) divide asymmetrically to self-renew and generate neurons either directly or indirectly via intermediate progenitor cells (IPCs, blue). The miR379–410 cluster miRNA miR-134 promotes neural precursor cell (NPC) proliferation whereas miR-369–3p, -496, -543 and -376a induce differentiation. Newborn neurons (beige) migrate along RGC processes into the cortical plate (CP) and reach their final destination via somal translocation. Neuronal migration is negatively regulated by the miR379–410 cluster miRNAs miR-134, -369–3p, -496 and -543. After settling, neurons initiate their terminal differentiation. MiR-134 and -485 negatively regulate spine density and maturation and miR-134, -381 and -329 enhance activity-dependent dendritogenesis. VZ, ventricular zone; SVZ, subventricular zone; IZ, intermediate zone; CP, cortical plate; green arrow, activation; red arrow, repression.

Conclusions and Outlook

It has been convincingly shown that miRNAs of the miR379–410 cluster are important regulators of various aspects of embryonic neurogenesis, neuronal migration and function (**Fig. 2**, **Table 1**). The knowledge acquired thus far, however, may only comprise the tip of the iceberg because only few miRNAs of the cluster have been studied and the available data is limited. Concerning neurogenesis the following open questions have to be addressed in the future: (i) are other miRNAs of the cluster involved in embryonic neurogenesis and (ii) are

miR379–410 cluster miRNAs also necessary for adult neurogenesis?

Mis-expression of the miRNAs of the cluster might contribute to the pathogenesis of neurodevelopmental disorders and neuropsychiatric diseases such as ID and autism that might be caused by failures of neurogenesis, neuronal migration or neuronal homeostasis. For example, the development of an ID in patients with upd(14)pat might be caused by the downregulation of the miR379–410 cluster miRNAs that are exclusively expressed from the maternal allele. Additional studies are needed to clarify these issues. While the mouse has proven to be a suitable model system to study the brain-specific functions of the miR379–410 cluster miRNAs, the development of induced pluripotent stem cell (iPSC) models may help to enhance our knowledge about miR379–410 cluster miRNA functions in humans.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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