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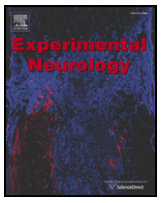

Review

MicroRNAs: Small molecules with big roles in neurodevelopment and diseases

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ABSTRACT

MicroRNAs (miRNAs) are single-stranded, non-coding RNA molecules that play important roles in the development and functions of the brain. Extensive studies have revealed critical roles for miRNAs in brain development and function. Dysregulation or altered expression of miRNAs is associated with abnormal brain development and pathogenesis of neurodevelopmental diseases. This review serves to highlight the versatile roles of these small RNA molecules in normal brain development and their association with neurodevelopmental disorders, in particular, two closely related neuropsychiatric disorders of neurodevelopmental origin, schizophrenia and bipolar disorder.

Contents

Introduction

MicroRNAs (miRNAs) are RNA molecules that belong to a family of small non-coding RNAs with 20 to 25 nucleotides (Ambros, 2004; Bartel, 2004). miRNAs post-transcriptionally regulate gene expression by binding to the 3′ untranslated region (3′ UTR) of their target messenger RNAs (mRNAs) through base-pairing, which in turn triggers mRNA degradation or translational inhibition. In mammalian cells, most miRNA genes are transcribed by RNA polymerase II (Pol II) to primary miRNAs (pri-miRNAs) that contain hundreds to thousands of nucleotides and extended hairpin structures (Bartel, 2004). Pri-miRNAs are further processed in the nucleus by Drosha and DiGeorge syndrome critical region gene 8 (DGCR8) to produce precursor miRNAs (pre-miRNAs) with stem-loop structure. Pre-miRNAs are exported into the cytoplasm by exportin-5/RanGTP and cleaved by Dicer to form mature miRNAs. These mature miRNAs are then loaded into the RNA-induced silencing complex (RISC), a ribonucleoprotein complex that is composed of the human immunodeficiency virus transactivating response RNA-binding protein (TRBP), Argonaute 2 (Ago2), and Dicer, to bind to the target mRNA to modulate gene expression (Bartel, 2004; Kim, 2005).

miRNAs have been shown to regulate a variety of biological processes, including development, cell proliferation and fate specification, growth control, and apoptosis (Gao, 2010; Lang and Shi, 2012; Li and Jin, 2010; Shi et al., 2010; Stefani and Slack, 2008). Extensive studies have implicated miRNAs in the regulation of brain development and

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Table 1
miRNAs involved in neurodevelopment and associated with schizophrenia (Scz) or bipolar disorder (BP).

miRNA	Targets	Function of miRNA	Reference
miR-9	TLX	Promote neuronal differentiation	Zhao, et al., (2009), Zhao, et al., (2013)
	FOXG1	Promote neuronal differentiation	Shibata, et al., (2008)
	HER5, HER9, CNPY1, FGF8 & FGFR1	Promote neuronal differentiation	Leucht, et al., (2008)
	REST	Promote neuronal differentiation	Laneve, et al., (2010), Packer, et al., (2008)
	SENSELESS	Promote neuronal differentiation	Li, et al., (2006)
	SIRT1	Promote neuronal differentiation	Saunders, et al., (2010)
	ID2	Promote neuronal differentiation	Annibali, et al., (2012)
	HDAC4	Promote neuronal differentiation	Davila, et al., (2014)
	HER6, ZIC5, ELAVL3	Promote neuronal differentiation & control neuronal production	Coolen, et al., (2012)
	HES1	Promote neuronal differentiation & control HES1 oscillation	Bonev, et al., (2012), Goodfellow, et al., (2014), Tan, et al., (2012)
	MCPIP1	Promote NPC proliferation & neuronal differentiation	Yang, et al., (2013)
	STMN1	Promote NSC proliferation	Delaloy, et al., (2010)
	HAIRY1	Promote NSC proliferation	Bonev, et al., (2011)
	FOXP1	Control motor neuron development	Otaegi, et al., (2011)
	ONECUT1	Specify motor neuron fate	Luxenhofer, et al., (2014)
	FOXP2	Promote neurite outgrowth & neuronal migration	Clovis, et al., (2012)
	MAP1B	Control axon extension & branching	Dajas-Bailador, et al., (2012)
	DRD2	Associated with Scz through DRD2	Shi, et al., (2014)
miR-124	SCP1	Promote neuronal differentiation	Visvanathan, et al., (2007)
	PTBP1	Promote neuronal differentiation	Makeyev, et al., (2007)
	SOX9	Promote neuronal differentiation	Cheng, et al., (2009)
	BAF53a	Promote neuronal differentiation	Yoo, et al., (2009)
	CREB1	Inhibit synaptic activity	Rajasethupathy, et al., (2009)
	LAMC1, ITGB1	Inhibit progenitor genes	Cao, et al., (2007)
	Ephrin-B1	Promote neuronal differentiation	Arvanitis, et al., (2010)
	NEUROD1	Promote NSC proliferation	Liu, et al., (2011)
	RHOG	Stimulate neuronal process complexity	
	JAG1	Promote neuronal fate determination	Akerblom, et al., (2012)
	ROCK1	Promote neurite outgrowth & elongation	Gu, et al., (2014)
	CoREST	Promote radial migration of projection neurons	Volvert, et al., (2014)
	EZH2	Promote neuronal differentiation & inhibit astrocyte differentiation	Neo, et al., (2014)
	EGR1	Regulate spatial learning & social interactions	Yang, et al., (2012)
	EGR1	Regulate synaptic transmission & cognition	Wang, et al., (2013)
	RGS4	Associated with Scz through RGS4	Gong, et al., (2013)
miR-137	LSD1	Promote neuronal differentiation	Sun, et al., (2011)
	EZH2	Promote NSC proliferation	Szulwach, et al., (2010)
	MIB1	Inhibit dendritic differentiation	Smrt, et al., (2010)
		Associated with Scz via the rs1625579 SNP	Ripke, et al., (2011)
	CACNA1C, TCF4, CSMD1, C10orf26, ZNF804A	Associated with Scz through these targets	Guan, et al., (2014), Kim, et al., (2012), Kwon, et al., (2013)
	MAD1L1, DPYD, BDNF	Associated with Scz through these targets	Hill, et al., (2014)
	CACNA1C	Associated with BP through CACNA1C	Ferreira, et al., (2008), Sklar, et al., (2008)
miR-219	PDGFRα, SOX6, FOXJ3, ZFP238	Promote oligodendrocyte differentiation	Dugas, et al., (2010)
	SOX6, HES5	Promote oligodendrocyte differentiation	Zhao, et al., (2010)
	PARD3, PRKCI	Promote neural precursor differentiation	Hudish, et al., (2013)
	SCOP	Attenuate NMDA-induced neuronal depolarization	Cheng, et al., (2007)
	CaMKIIγ	Regulate pain behavior	Pan, et al., (2014)
	CaMKIIγ	Associated with Scz through regulating NMDA receptor signaling	Kocerha, et al., (2009)
		Associated with Scz and BP as revealed by elevated expression in these patients	Beveridge, et al., (2010), Smalheiser, et al., (2014)
miR-132	p250GAP	Promote dendritic development	Impey, et al., (2010), Pathania, et al., (2012), Wayman, et al., (2008)
	MeCP2	Regulate dendritic morphology	Klein, et al., (2007)
		Mediate the integration of newborn neurons	Luikart, et al., (2011)
		Regulates synaptic plasticity & recognition memory	Hansen, et al., (2013), Hansen, et al., (2010), Lambert, et al., (2010), Scott, et al., (2012)
	RASA1	Promote axon extension	Hancock, et al., (2014)
	RFX4	Potentiate NMDA receptor depolarization	Cheng, et al., (2007)
	DNMT3A, GATA2, DPYSL3	Associated with Scz as revealed by reduced expression in the patients	Miller, et al., (2012)
miR-17 family	p38	Inhibit neurogenic to gliogenic transition	Naka-Kaneda, et al., (2014)
	BMPR2	Promote neural precursor cell proliferation	Mao, et al., (2014)
	TRP53INP1	Enhance NSC self-renewal	Garg, et al., (2013)
	PTEN and TBR2	Control spinal neural progenitor patterning	Bian, et al., (2013)
	OLIG2	Regulate spinal neural progenitor patterning	Chen, et al., (2011)
	NPAS3	Associated with Scz as revealed by elevated expression in the patients	Santarelli, et al., (2011), Wong, et al., (2013)
		Associated with Scz as revealed by higher serum level in sporadic patients	Shi, et al., (2012)
miR-200 family	SPITZ	Control neuroepithelial expansion and neuroblast transition	Morante, et al., (2013)
	ZEB	Repress neural induction from embryonic stem cells	Du, et al., (2013)
	SOX2, E2F3	Promote neural progenitor cell-cycle exit & neuronal differentiation	Peng, et al., (2012)
	FOXG1, ZFHX1, LFNG	Maintain olfactory neurogenesis	Choi, et al., (2008)
miR-195	MBD1	Enhance neural stem cell proliferation and repress differentiation	Liu, et al., (2013)
		Associated with Scz as revealed by decreased expression in the patients	Perkins, et al., (2007)
	BDNF	Regulates BDNF-related GABAergic gene transcripts in Scz subjects	Mellios, et al., (2009)
		Associated with Scz as revealed by higher serum level in sporadic patients	Shi, et al., (2012)

The function of miRNAs in neurodevelopment is listed in gray and white boxes, whereas the association with Scz and BP is indicated in orange and white boxes. SIRT1: sirtuin 1; ID2: inhibitor of DNA binding 2; HDAC4: histone deacetylase 4; HER6: hairy-related 6; ZIC5: Zic family member 5; ELAVL3: ELAV (embryonic lethal, abnormal vision)-like protein 3; MCPIP1: monocyte chemotactic protein-induced protein 1; STMN1: stathmin 1; NEUROD1: neurogenic differentiation 1; JAG1: jagged 1; CoREST: corepressor of REST; MAD1L1: MAD1 mitotic arrest deficient-like 1; DPYD: dihydropyrimidine dehydrogenase; BDNF: brain-derived neurotrophic factor; PDGFRα: platelet-derived growth factor receptor α; SOX6: SRY box 6; FOXJ3: forkhead box protein J3; ZFP238: zinc finger protein 238; HES5: hairy and enhancer of split-5; SCOP: suprachiasmatic nucleus circadian oscillatory protein; RASA1: RAS p21 protein activator 1; RFX4: regulatory factor X, 4; DNMT3A: DNA-methyltransferase 3A; GATA2: GATA binding protein 2; DPYSL3: dihydropyrimidinase-like 3; p38: p38 mitogen-activated protein kinase; BMPR2: bone morphogenetic protein receptor type II; TRP53INP1: transformation related protein 53 inducible nuclear protein 1; PTEN: phosphatase and tensin homolog; TBR2: T-box brain protein 2; OLIG2: oligodendrocyte transcription factor 2; NPAS3: neuronal PAS domain protein 3; ZEB: zinc-finger E-box-binding homeobox; Sox2: SRY box 2; E2F3: E2F transcription factor 3; ZFHX1: zinc finger homeobox 1; LFNG: lunatic fringe; MBD1: methyl-CpG-binding domain protein 1.

neurogenesis (Kosik, 2006; Kosik and Krichevsky, 2005; Lang and Shi, 2012; Li and Jin, 2010; Shi et al., 2008, 2010). Precise regulation of miRNA expression is required for normal brain development, whereas dysregulation of miRNA expression and function has been implicated in the pathogenesis of a variety of neurological diseases, including neurodevelopmental disorders and neurodegenerative diseases (Bian

and Sun, 2011; Qurashi and Jin, 2010). This review will discuss recent progress on understanding the roles of miRNAs in normal brain development and the association of these miRNAs with neurodevelopmental diseases, specifically schizophrenia and bipolar disorder, two closely related disorders (Table 1).

miRNAs in neurodevelopment

Studies using animal models with deficiency in miRNA biogenesis have revealed essential roles for miRNAs in brain development and function. For example, Ago2-deficient mice exhibited defects in neural tube closure and mis-patterning of the forebrain (Liu et al., 2004). Loss of Dicer in zebrafish skewed brain development and the abnormal brain phenotype could be rescued by introducing a miRNA, miR-430 (Giraldez et al., 2005). Conditional knockout of Dicer in mouse neural stem cells led to smaller cortex (De Pietri Tonelli et al., 2008), presumably because deletion of Dicer interfered with neural stem cell expansion and differentiation (Andersson et al., 2010; Kawase-Koga et al., 2010). Loss of Dicer expression in neurons caused abnormal neuronal maturation, including reduced dendritic arborization and defective axonal path finding (Davis et al., 2008). Deletion of Dicer in dopaminergic neurons resulted in progressive loss of midbrain dopaminergic neurons and Parkinson-like symptoms in mice (Cuellar et al., 2008; Kim et al., 2007). Together, these studies demonstrate important roles for miRNAs in neurodevelopment.

Several brain-specific or brain-enriched miRNAs have been identified and characterized. The brain-specific miRNA miR-9 has been extensively studied in neurogenesis. We have shown that there is a feedback regulatory loop between miR-9 and the nuclear receptor TLX during neural stem cell differentiation (Zhao et al., 2009). TLX plays an essential role in maintaining neural stem cells in the proliferative and self-renewable state (Liu et al., 2008; Qu et al., 2010; Shi et al., 2004; Zhang et al., 2008). miR-9 inhibits the expression of TLX by base-pairing to the 3′ UTR of TLX mRNA (Zhao et al., 2009), which in turn reduces neural stem cell proliferation and promotes neural differentiation. On the other hand, TLX represses the expression of miR-9 pri-miRNAs by binding to their genomic loci (Zhao et al., 2009). An inverse correlation was also observed between TLX and miR-9 expression in neural stem cells and transit amplifying progenitors (Obernier et al., 2011). The miR-9-TLX regulatory loop thus provides a precise control over neural stem cell fate determination. Recently we showed that the cascade of TLX and miR-9 acts downstream of let-7 family microRNAs let-7b and let-7d, to regulate neurogenesis (Zhao et al., 2009, 2010a, 2013). A regulatory loop between miR-9 and REST (RE1-silencing transcription factor) was also observed during neural differentiation (Laneve et al., 2010; Packer et al., 2008). Recently, a negative feedback circuit between miR-9 and hairy and enhancer of split 1 (Hes1) was described, in which the input of miR-9 into the Hes1 oscillator controls the timing of neural progenitor cell differentiation and cell fate determination (Goodfellow et al., 2014).

Congruent with its role in promoting differentiation of neural stem cells (Zhao et al., 2009), miR-9 triggers neural differentiation from embryonic stem cells as well (Saunders et al., 2010). The pro-differentiation role of miR-9 is also evident in the observation that miR-9 promotes Cajal–Retzius neuronal differentiation by targeting forkhead box protein G1 (FoxG1) expression (Shibata et al., 2008). miR-9 also promotes the differentiation and axonal projection of spinal motoneurons by targeting forkhead box protein P1 (FoxP1) (Otaegi et al., 2011) and specifies motor neuron fate by regulating onecut homeobox 1 expression (Luxenhofer et al., 2014). Moreover, miR-9 inhibits the expression of forkhead box protein P2 (FoxP2) to promote the migration and maturation of cortical neurons (Clovis et al., 2012). This miRNA could also regulate neuronal maturation by modulating the expression of microtubule-associated protein 1b (Map1b) (Dajas-Bailador et al., 2012). The observation that miR-9/9* together with miR-124 was able to convert human fibroblast cells into functional neurons reinforces the essential role of miR-9 in neuronal differentiation (Yoo et al., 2011).

In developing zebrafish, miR-9 induces neurogenesis by targeting the expression of hairy-related 5 (her5), hairy-related 9 (her9), canopy1 (cnpy1), fibroblast growth factor 8 (fgf8), and fibroblast growth factor receptor 1 (fgfr1) (Leucht et al., 2008). In *Xenopus* brains, miR-9 inhibits neural progenitor cell proliferation and apoptosis by suppressing the expression of Hairy 1, a member of the Hes (hairy and enhancer of split) family genes (Bonev et al., 2011). In miR-9-2/3 knockout mice, in which two of the miR-9 genomic loci (miR-9-2 and miR-9-3) were mutated, miR-9 was shown to regulate both neural progenitor proliferation and differentiation in a cellular context-specific manner (Shibata et al., 2011). In addition to its major role in inhibiting neural stem cell proliferation and promoting neural differentiation, miR-9 also participates in neural progenitor cell expansion at an early stage (Delaloy et al., 2010).

miR-124 is a miRNA that is specifically expressed in the central nervous system (Deo et al., 2006; Lagos-Quintana et al., 2002) and mostly expressed in post-mitotic neurons (Akerblom et al., 2012; Maiorano and Mallamaci, 2009). The expression of miR-124 increases during brain development (Krichevsky et al., 2003, 2006; Sempere et al., 2004; Smirnova et al., 2005). miR-124 promotes neuronal differentiation by targeting genes such as small CTD phosphatases 1 (SCP1) (Visvanathan et al., 2007), laminin gamma 1 (LAMC1) and integrin beta 1 (ITGB1) (Cao et al., 2007), BAF complex 53 kDa subunit (BAF53a) (Yoo et al., 2009), SRY-box containing gene 9 (Sox9) (Cheng et al., 2009), polypyrimidine tract binding protein 1 (PTBP1) (Makeyev et al., 2007), and ephrin-B1 (Arvanitis et al., 2010). In addition to its role in neuronal differentiation, miR-124 regulates neuronal maturation by targeting the expression of cAMP response element-binding protein (CREB) (Rajasethupathy et al., 2009), LIM/homeobox protein 2 (Lhx2) (Sanuki et al., 2011), Rho-associated coiled-coil-containing protein kinase 1 (ROCK1) (Gu et al., 2014), and the small GTPase Ras homolog growth-related (RhoG) (Franke et al., 2012). Recently, miR-124 was shown to regulate synaptic transmission and cognition by inhibiting the expression of early growth response gene 1 (Egr1) (Wang et al., 2013; Yang et al., 2012).

Ectopic expression of miR-124 in HeLa cells was shown to suppress non-neuronal genes but stimulate neuronal genes, suggesting that miR-124 has a pro-neuronal role (Lim et al., 2005). The observation that viral transduction of miR-124 into human fibroblast cells along with miR-9/9* or myelin transcription factor 1-like (MYT1L) and POU class 3 homeobox 2 (POU3F2 or BRN2) converted these cells into functional neurons further supports the essential role of miR-124 in neuronal differentiation (Ambasudhan et al., 2011; Yoo et al., 2011). These studies together highlight the importance of miR-124 in neuronal differentiation.

The brain-enriched miRNA miR-137 also plays a pro-differentiation role in neural stem cells from the ventricular zone of embryonic mouse brains (Sun et al., 2011) and the subventricular zone of adult mouse brains (Silber et al., 2008). Increased expression of miR-137 led to reduced neural stem cell proliferation and increased neural differentiation. A regulatory loop of TLX-miR-137-lysine-specific histone demethylase 1(LSD1) ensures the coordinated expression of TLX/LSD1 and miR-137 during the transition of neural stem cell proliferation and differentiation, and provides a mechanism to control the dynamics between cell proliferation and differentiation (Sun et al., 2011).

In another study, miR-137 was shown to regulate adult hippocampal neurogenesis by targeting the enhancer of zeste homolog 2 (Ezh2) (Szulwach et al., 2010), a histone methyltransferase that is important in maintaining the bivalent chromatin state of stem cells (Boyer et al., 2006). In addition, miR-137 reduces neuronal maturation by targeting a ubiquitin ligase, mindbomb homolog 1 (Mib1) (Smrt et al., 2010). Single-nucleotide polymorphism (SNP) in miR-137 and its target genes have been associated with schizophrenia (Ripke et al., 2011), presumably due to dysregulation of neurodevelopment.

miR-219 is a miRNA that is specifically expressed in mammalian brains (Cheng et al., 2007; Lukiw, 2007). Brain specific expression of miR-219 was also observed in zebrafish (Kapsimali et al., 2007). It has been shown that miR-219 is both necessary and sufficient to promote oligodendrocyte differentiation in mouse and zebrafish by repressing negative regulators of oligodendrocyte differentiation (Dugas et al., 2010; Zhao et al., 2010b). In a recent study, miR-219 was shown to promote neural precursor cell differentiation in zebrafish spinal cord by inhibiting apical polarity proteins, par-3 family cell polarity regulator (PARD) and protein kinase C, iota (PRKCI) (Hudish et al., 2013). Moreover, miR-219 regulates pain behavior in mouse spinal neurons by targeting calcium/calmodulin-dependent protein kinase II γ subunit (CaMKIIγ) and regulating N-methyl-D-aspartate (NMDA) receptor signaling transduction (Pan et al., 2014). Since interference with NMDA-mediated glutamate signaling has been linked to behavioral deficits in schizophrenia, an association between miR-219 and schizophrenia has been suggested, which will be discussed in the next section.

miR-132 is an activity-dependent miRNA that plays an important role in neuronal plasticity, synaptic physiology and memory. Overexpression of miR-132 in primary cortical, hippocampal and olfactory bulb neurons promoted neurite outgrowth, enhanced dendritic length and complexity, and stimulated activity-dependent spine formation, whereas inhibition of miR-132 or deletion of the miR-132/212 locus induced opposite effects (Edbauer et al., 2010; Impey et al., 2010; Magill et al., 2010; Pathania et al., 2012; Vo et al., 2005; Wayman et al., 2008). The effect of miR-132 on dendritic morphogenesis is mediated in part by targeting p250GAP (Rho GTPase-activating protein 32), which in turn activates RAC1 (a Rho family, small GTP binding protein)-PAK (the p21-activated kinase)-mediated spinogenesis (Impey et al., 2010; Wayman et al., 2008). miR-132 was also reported to target methyl CpG-binding protein 2 (MeCP2), a regulator of dendritic morphology and synapse formation (Klein et al., 2007). In addition to neuronal morphology, miR-132 regulates newborn neuron integration and synaptic transmission. Overexpression of miR-132 increased paired-pulse ratio, a measure for changes in presynaptic release probability, and decreased synaptic depression (Lambert et al., 2010), whereas inhibition or knockout of miR-132 impaired the integration of newborn neurons into the excitatory synaptic circuitry, reduced the frequency of miniature excitatory post-synaptic currents (mEPSCs), and blunted basal synaptic transmission (Impey et al., 2010; Luikart et al., 2011; Remenyi et al., 2013). Recently it was shown that miR-132 expression was modulated by visual experience, and miR-132 in turn regulated visual cortex plasticity (Mellios et al., 2011; Tognini et al., 2011). A link between miR-132 expression and cognition has also been established. Transgenic overexpression of miR-132 in the forebrain impaired recognition memory (Hansen et al., 2010; Scott et al., 2012). In contrast, induced expression of endogenous miR-132 in response to a spatial memory task enhanced cognition (Hansen et al., 2013), suggests that the expression level of miR-132 is tightly regulated to control learning and memory (Bicker et al., 2014). The expression of miR-132 is dysregulated in a number of neurodevelopmental disorders (Kim et al., 2010; Klein et al., 2007; Packer et al., 2008). The knowledge on miR-132 expression and function in normal neurodevelopment may shed light on the pathological origins of the neurodevelopmental diseases.

miRNAs in schizophrenia

Multiple studies suggest that defective neuronal plasticity and function in neurodevelopmental disorders may have resulted from impaired posttranscriptional regulation mediated by miRNAs (Hunsberger et al., 2009). Increasing evidence suggests that miRNAs play important roles in the etiology of neuropsychiatric, neurodevelopmental disorders, and neurodegenerative diseases (Olde Loohuis et al., 2012).

Schizophrenia is a devastating neuropsychiatric disorder of neurodevelopmental origin, arising through complex interplay between genetic and epigenetic factors (Harrison, 1997). Although schizophrenia is considered largely heritable, with an estimated rate of heritability about 80%, the effect of susceptibility genes has been small (Purcell et al., 2009). Because miRNAs play essential roles in brain development and have the ability to target multiple genes, the potential roles for miRNAs in the abnormal brain development in schizophrenia have been investigated (Kolshus et al., 2013). Interestingly, patients with DiGeorge 22q11.2 deletion, which affects a key miRNA processing gene DGCR8, showed a 30-fold increase in the risk of schizophrenia (Stark et al., 2008). A hot spot for neurodevelopmental disorders, including schizophrenia, has also been described on chromosome 8p, in which at least seven miRNAs are located (Tabares-Seisdedos and Rubenstein, 2009).

The largest Genome-Wide Association Study (GWAS) in schizophrenia with more than 40,000 individuals, revealed that the strongest association of SNP with schizophrenia laywithin the intron of a putative primary transcript for miR-137 (Ripke et al., 2011), a known regulator of neurodevelopment (Silber et al., 2008; Smrt et al., 2010; Sun et al., 2011). This association was confirmed in other independent association studies (Green et al., 2013; Potkin et al., 2009). Other schizophrenia SNPs that achieved genome-wide significance include several miR-137 target genes, including transcription factor 4 (TCF4), calcium channel, voltage-dependent, L type, alpha 1C subunit (CACNA1C), CUB and Sushi multiple domains 1 (CSMD1), chromosome 10 open reading frame 26 (C10orf26), and zinc finger protein 804A (ZNF804A) (Kim et al., 2012; Kwon et al., 2013; Ripke et al., 2011). Subsequent studies revealed that variation in miR-137 specifically affected brain activation and functional connectivity in individuals with genetic/familial risk of schizophrenia, but not in control subjects (Mothersill et al., 2014; Whalley et al., 2012). The essential role of miR-137 in neurodevelopment and its association with schizophrenia reinforces the concept that schizophrenia is a disorder of neurodevelopment. Microdeletion of chromosome region containing the miR-137 gene has also been linked to intellectual disability (Willemsen et al., 2011). Moreover, SNP in other miRNAs, such as miR-206, miR-198, and miR-30e, have also been associated with schizophrenia in different ethnic groups (Feng et al., 2009; Hansen et al., 2007; Xu et al., 2010).

In addition to SNP in miRNAs, SNP in target genes of different miRNAs have been identified. For example, the SNP rs10759 (A > C) in the regulator of G protein signaling 4 (RGS4) gene, a downstream target of miR-124, is predicted to increase the risk of schizophrenia (Gong et al., 2013). Decreased expression of RGS4 has been observed in the frontal cortex and superior temporal gyrus of schizophrenia patients (Bowden et al., 2007; Erdely et al., 2006). The rs10759 SNP changes the binding of miR-124 to RGS4. miR-124 inhibits the expression of RGS4 by binding to the 3′ UTR of RGS4 with rs10759 (C), but does not bind to the 3′ UTR of RGS4 with rs10759 (A) (Gong et al., 2013). The dopamine receptor D2 (DRD2) gene, a downstream target of miR-9, is also implicated in the pathophysiology of schizophrenia. The SNP rs1801028 (Cys311Ser) in DRD2 is linked to schizophrenia in a meta-analysis (Glatt et al., 2003; Shi et al., 2014). An inverse correlation in the expression of DRD2 and miR-9 has been observed in regions of human brains implicated in schizophrenia (Shi et al., 2014). The pathological significance of miR-9 and miR-124 and their relevant target genes in schizophrenia is worthy of further investigation.

Several studies analyzed miRNA levels in postmortem brains from schizophrenia patients and identified multiple miRNAs that are differentially expressed (Beveridge et al., 2008, 2010; Burmistrova et al., 2007; Kim et al., 2010; Mellios et al., 2009, 2012; Miller et al., 2012; Moreau et al., 2011; Perkins et al., 2007; Santarelli et al., 2011; Wong et al., 2013; Zhu et al., 2009). Some of these dysregulated miRNAs could modulate the expression of genes associated with schizophrenia (Kocerha et al., 2009; Miller et al., 2012). Initial studies on postmortem brains revealed an overall decrease in miRNA expression in the prefrontal cortex of schizophrenia patients (Perkins et al., 2005, 2007). These miRNAs include miR-26b, miR-29b, miR-30b, and miR-106b. A subsequent independent study showed that the expression of

miR-132 and miR-132* was significantly decreased in brains of schizophrenia patients (Miller et al., 2012). miR-132 has been shown to potentiate NMDA receptor depolarization (Cheng et al., 2007). The reduced expression of miR-132 in schizophrenia patients is consistent with the hypofunction of the NMDA receptor in schizophrenia patients.

Later studies reported an increase in the expression of a set of miRNAs in medial temporal regions of schizophrenia patients (Beveridge et al., 2008, 2010; Santarelli et al., 2011), coinciding with elevated expression of components in the miRNA biogenesis machinery (Beveridge et al., 2008, 2010; Santarelli et al., 2011). The upregulated miRNAs include miR-219, miR-181b, and miR-15 family members (Beveridge et al., 2008, 2010). Of interest, miR-219 functions to mediate the behavioral effects of Dizocilpine, an antagonist of the N-methyl-D-aspartate (NMDA) receptor (Kocerha et al., 2009). Acute treatment with Dizocilpine decreased the levels of miR-219 in the prefrontal cortex, whereas inhibition of miR-219 action suppressed Dizocilpine-induced hyperlocomotion and stereotypies. Thus, elevated expression of miR-219 in the dorsolateral prefrontal cortex from schizophrenia patients (Beveridge et al., 2010; Smalheiser et al., 2014) is consistent with the NMDA receptor hypoactivity theory of schizophrenia (Miller and Wahlestedt, 2010). Manipulating the expression or activity of miR-219 may therefore provide a potential therapeutic tool for the treatment of schizophrenia.

miRNAs in bipolar disorder

Bipolar disorder is a severe neuropsychiatric disease characterized by mood swings between mania and depression. Although they are two disease entities, bipolar disorder and schizophrenia have many overlapping symptoms. Moreover, these two disorders are frequently concurrent in affected families and have similar epidemiological risks (Lichtenstein et al., 2009; Purcell et al., 2009). Indeed, bipolar disorder shares genetic risk factors with schizophrenia and, like schizophrenia, has an estimated heritability rate of 70–80% (Kolshus et al., 2013). As in schizophrenia, the problem of multiple susceptibility genes of small effect has led to an increased interest in defining the roles of miRNAs in bipolar disorder because one miRNA can target hundreds of genes.

Most miRNA studies in bipolar disorder used postmortem samples, many of which included schizophrenia subjects (Kolshus et al., 2013). Several of these studies identified overlapped change in miRNA levels between bipolar disorder and schizophrenia (Kim et al., 2010; Moreau et al., 2011), suggesting common molecular basis shared by these diseases (Purcell et al., 2009). In a study on patients with bipolar disorder, schizophrenia, and psychiatrically normal control subjects, all miRNAs that have reduced expression in the schizophrenia patient group (relative to control subjects) also exhibit reduced expression in the bipolar disorder patient group. These miRNAs include miR-15a, miR-22, miR-33, miR-106b, miR-138, miR-151, miR-210, miR-324-5p, miR-338, miR-339 and miR-425 (Moreau et al., 2011). On the other hand, some miRNAs such as miR-219, exhibited elevated expression in the prefrontal cortex of both schizophrenia and bipolar disorder patients relative to the control group (Smalheiser et al., 2014).

Patients with bipolar disorder are usually treated with mood stabilizers, including lithium and valporate (Bowden et al., 1994; Pope et al., 1991). It has been shown that several miRNAs, including let-7b, let-7c, miR-128a, miR-24a, miR-30c, miR-34a, and miR-221, were upregulated after treatment with the mood stabilizers, lithium and valporate (Zhou et al., 2009). In an effort to identify peripheral biomarkers for bipolar disorder, miR-134 was identified as a blood marker of clinical status in bipolar disorder patients (Rong et al., 2011). Both in drug-free and medicated patients, a negative correlation was observed between miR-134 levels and manic symptoms (Rong et al., 2011). These studies suggest that miRNAs have the potential to serve as both therapeutic targets and biomarkers for bipolar disorders.

Perspectives

This review aims to emphasize the significance of miRNAs in neurodevelopment and summarize the potential link between dysregulated miRNAs and the etiology of two related neurodevelopmental disorders, schizophrenia and bipolar disorder. Defining the role of these miRNAs in normal neurodevelopment may help us to probe the pathological mechanisms of related neurodevelopmental disorders. Although we are still at the infant stage of genetic studies on miRNA-related genes, the recent annotation of new miRNA SNPs paves the road for growing research interest in this field. Next generation sequencing (NGS) technology will allow rapid development in this area. New miRNAs will also be identified due to the development of NGS, which will paint a more comprehensive picture of miRNA networks in brain development and disorders. Such picture will improve our understanding on the molecular mechanisms underlying the phenotypes of neurodevelopmental diseases, and ultimately lead to the development of more effective therapies for these disorders by targeting relevant miRNAs and their target genes.

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