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Review

MicroRNA dysregulation in neuropsychiatric disorders and cognitive dysfunction

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ABSTRACT

MicroRNAs (miRNA), a class of non-coding RNAs, are emerging as important modulators of neuronal development, structure and function. A connection has been established between abnormalities in miRNA expression and miRNA-mediated gene regulation and psychiatric and neurodevelopmental disorders as well as cognitive dysfunction. Establishment of this connection has been driven by progress in elucidating the genetic etiology of these phenotypes and has provided a context to interpret additional supporting evidence accumulating from parallel expression profiling studies in brains and peripheral blood of patients. Here we review relevant evidence that supports this connection and explore possible mechanisms that underlie the contribution of individual miRNAs and miRNA-related pathways to the pathogenesis and pathophysiology of these complex clinical phenotypes. The existing evidence provides useful hypotheses for further investigation as well as important clues for identifying novel therapeutic targets.

Contents

Introduction

Non-coding RNAs (ncRNAs), transcribed RNAs that are not further translated into proteins, play an important regulatory role in shaping protein production and are an integral part of the epigenetic network. One class of ncRNAs that has been extensively studied in recent years

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is miRNAs, which are about 22 nucleotides long (Bartel, 2004). miRNAs regulate gene expression primarily through post-transcriptional gene silencing by complementary binding to their target mRNAs (Lewis et al., 2003). The interaction of miRNAs with their target mRNAs is largely through 5′ seed region of the miRNA and one or more binding sites in the 3′UTR of the targets, though it is shown that the interaction can be mediated through other regions. This interaction directs miRNA-associated complexes to mediate translational repression and/or mRNA degradation (Prosser et al., 2011). Since the interaction of miRNAs and their mRNA targets is primarily determined by the short seed region encompassing only 6–8 nucleotides, one miRNA typically has multiple mRNA targets (Lewis et al., 2005) while several miRNAs can bind on the same mRNA target. Therefore, miRNAs can thus act in combinatorial or synergistic fashion by integrating different intracellular signals and/or coordinating several different signaling pathways at once (Krek et al., 2005). Furthermore, the production of miRNAs is regulated at various steps during biogenesis, both at transcription and post-transcriptional levels (Krol et al., 2010b). Importantly, miRNAs can incorporate into different RNA-binding protein complexes, which provide information for subcellular localization and control the accessibility of potential targets at different intracellular locations. Genuine interaction between a miRNA and its targets can be experimentally detected and validated by either indirect methods, such as luciferase assays or by more direct approaches such as high-throughput sequencing of RNA isolated by crosslinking and immunoprecipitation (HITS-CLIP) (Chi et al., 2009) and Tandem affinity purification of miRNA target mRNAs (TAP-Tar) (Brest et al., 2011) (reviewed by (Thomson et al., 2011). More recently a resource of mouse targeted miRNA knockout embryonic stem cells has been generated (Prosser et al., 2011). Studies utilizing such approaches and resources are poised provide a comprehensive understanding the role that miRNAs play in animal development and disease.

Overall, miRNA provide great control flexibility by integrating signals from different pathways under a variety of physiological conditions and, therefore, can have a great impact on neuronal function and communication (Cao et al., 2006). Along these lines, it is becoming increasingly clear that miRNAs have a profound impact on cognitive function and are involved in the etiology of several neuropsychiatric disorders, including schizophrenia, mental retardation (or intellectual disability) as well as autism and autism spectrum disorders. Here, we first summarize relevant evidence from human and animal model studies and then we discuss the contribution of some of the altered miRNAs to various neural processes that can potential impact psychiatric disease pathophysiology.

Altered miRNA expression and function in various neuropsychiatric disorders

Accumulating evidence from human and animal studies strongly suggests that alterations in miRNA regulation or function associate with the genetic architecture of neuropsychiatric disorders including schizophrenia, autism and various forms of intellectual dysfunction as summarized below.

Schizophrenia

Schizophrenia (SCZ) is one of the most common psychiatric disorders with a prevalence of ~1% in most of the populations studied worldwide (Xu et al., 2011). SCZ is a disabling disease, which is characterized by positive (psychotic) symptoms such as hallucinations, delusions, and disorganized behavior, negative symptoms such as social withdrawal and apathy, as well as increasingly recognized cognitive deficits (Arguello et al., 2010). Classical family, twin, and adoption studies estimating the recurrence risk to relatives have provided direct evidence for a genetic etiology. The risk of developing SCZ increases exponentially with the degree of genetic relatedness to a patient and reaches ~50% for a monozygotic twin (Sullivan et al., 2003).

miRNA profiling in postmortem brain tissues from individuals with SCZ has shown alterations in the levels of many miRNAs (Beveridge et al., 2008, 2010; Kim et al., 2010; Moreau et al., 2011; Perkins et al., 2007; Santarelli et al., 2011) (see also below). However miRNA dysregulation in the disease brain is not specific to SCZ and has been described in a variety of other psychiatric, neurodevelopmental and neurological disorders (Abu-Elneel et al., 2008; Kuhn et al., 2008; Talebizadeh et al., 2008). Given the important role that miRNA play in posttranscriptional gene regulation and their potential to regulate a large number of target genes, the majority of the observed changes likely reflect reactive changes due to the disease state or medication. Such changes cannot be interpreted as indicative of a role of miRNAs in the disease pathogenesis and pathophysiology. Given the strong genetic component of SCZ, conclusive evidence that miRNAs might be one of the important components of the etiology and pathophysiology of SCZ can only be obtained by analyzing the impact that well established mutations or proximal processes affected by them (Kvajo et al., 2010) have on the formation, steady-state levels and function of miRNAs. In that respect it is notable that the most important insight into the relationship between SCZ etiology and miRNAs comes from recent studies on a mouse model of the 22q11.2 microdeletion (Stark et al., 2008), a well established and largest known genetic risk factor for schizophrenia (Karayiorgou et al., 2010; Xu et al., 2010).

The 22q11.2 microdeletion is a major recurrent de novo copy number variant (CNV) responsible for introducing new SCZ cases in the population (ISC, 2008; Karayiorgou et al., 1995; Stefansson et al., 2008; Xu et al., 2008a, 2009). A 1.5-Mb human 22q11.2 region has been shown to be the critical region for 22q11.2 microdeletion syndrome. Because this 1.5-Mb region is highly conserved in the syntenic region of mouse chromosome 16 and harbors nearly all ortholog of the human genes, a mouse model carrying the microdeletion ($Df(16)A^{+/-}$) was generated to investigate the abnormalities at different levels (Drew et al., 2011). $Df(16)A^{+/-}$ mice exhibit a variety of structural, behavioral, and cognitive alterations that are correlated with neuroanatomical abnormalities and cognitive dysfunction found in individuals with 22q11.2 microdeletions. For example, disruption of prepulse inhibition (PPI), a measure of sensorimotor gating and preattentive processes, is observed in both $Df(16)A^{+/-}$ mice (Stark et al., 2008) and individuals with 22q11.2 microdeletions(Ornitz et al., 1986; Sobin et al., 2005). In addition aspects of cognitive dysfunction in 22q11.2 microdeletion carriers (Casey et al., 1995) (Lajiness-O'Neill et al., 2005; Shprintzen et al., 1978) are also observed in $Df(16)A^{+/-}$ mice, as demonstrated by decreased accuracy in delayed non-match to place (DNMP) task of spatial working memory and deficits in both cued and contextual fear conditioning (Stark et al., 2008). Morphological analysis reveals that the CA1 neurons of $Df(16)A^{+/-}$ animals have simplified dendritic trees and decreased spine density (Mukai et al., 2008), which may partially account for reduction in hippocampal volume (Campbell et al., 2006; Eliez et al., 2000; Simon et al., 2005) in individuals with 22q11.2 microdeletions. Moreover, altered neural synchrony between dorsal hippocampus (HPC) and medial prefrontal cortex (PFC), as compared to WT mice (Sigurdsson et al., 2010) is consistent with PFC–HPC coupling abnormalities observed in schizophrenia patients (Ford et al., 2002; Lawrie et al., 2002; Meyer-Lindenberg et al., 2005). Although additional comparative analysis is necessary, results so far outline a number of conserved anomalies in hippocampal and frontal circuitry in 22q11.2 microdeletion carriers and the $Df(16)A^{+/-}$ mouse model (Drew et al., 2011; Karayiorgou et al., 2010) and provide a reliable model to interrogate the effects of miRNA dysregulation on neural circuit structure and function in a disease context.

mRNA and miRNA profiling indicated that miRNA alterations represent a major changes in *Df(16)A*$^{+/-}$ mice. *Dgcr8* gene, an important component of the miRNA biogenesis, is located within the 1.5-Mb microdeletion region (Stark et al., 2008). Stark et al. showed that the hemizygous deletion of the *Dgcr8* gene is the cause of downregulation (by ~20–70%) of 10–20% of all known mature miRNAs, including a number of miRNA clusters involved in neural development (see Insights from disruption of individual miRNAs) (Stark et al., 2008). In addition to *Dgcr8*, the 22q11.2 microdeletion and the equivalent mouse deficiency also remove one copy of a miRNA gene, *miR-185*, located within the minimal 1.5-Mb 22q11.2 critical region.

Compelling evidence for miRNA dysregulation due to 22q11.2 microdeletions provides a useful etiological context to interpret results obtained from ongoing studies monitoring miRNA expression changes in the brains and peripheral blood cells in schizophrenia. For example, two recent studies provide supporting evidence suggesting that miRNAs dysregulated as a result of the 22q11.2 microdeletion may have a more general role in SCZ pathogenesis (Fig. 1). Moreau MP et al. tested 435 miRNAs and 18 small nucleolar RNAs in the Brodmann area 9 of the prefrontal cortex using real-time quantitative PCR. After controlling for confounding variables such as sample storage time, brain pH, alcohol at time of death, and postmortem interval, 19% of analyzed miRNAs exhibited altered expression associated with diagnosis of SCZ or bipolar disorder and both conditions

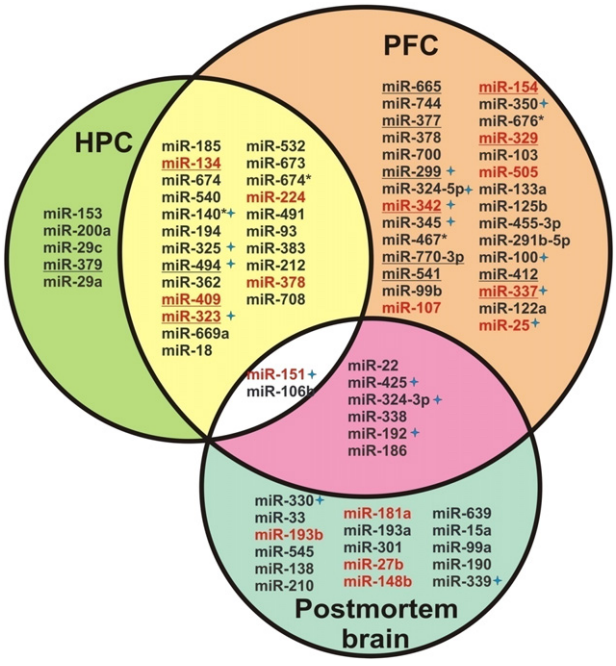

Fig. 1. Convergent downregulation of miRNAs in schizophrenia patients and *Df(16)A*$^{+/-}$ mice. In *Df(16)A*$^{+/-}$ mice, expression of 30 miRNAs in HPC and 60 miRNAs in PFC is reduced due to hemizygosity of *Dgcr8* gene. Among them 25 miRNAs are downregulated in both HPC and PFC. In a study of postmortem brain samples from patients with SCZ or bipolar disorder (BP), Moreau et al. identified 24 dysregulated miRNAs (having >95% posterior probability of nonzero effect of psychiatric diagnosis). Among those, 8 are down-regulated in the PFC of *Df(16)A*$^{+/-}$ mice, including miR-151 and miR-106b that are downregulated in the HPC as well (Moreau et al., 2011). In addition, miRNA profiling in PBMC of patients with SCZ found 83 miRNAs downregulated with a false discovery rate (FDR) <5% (Gardiner et al., 2011). Interestingly, 15 miRNAs, including miR-134, are transcribed and possibly co-regulated from the maternally expressed *DLK1-DIO3* locus on chromosome 14q32 (a homologous locus on mouse chromosome 12qF1), suggesting that fine control of miRNA expression from this locus may be critical for normal brain development and function. MiRNAs identified as downregulated in both the Gardiner et al. study and the *Df(16)A*$^{+/-}$ mice are shown in RED. Overlapping miRNAs located in the DLK1-DIO3 locus are underlined. It is important to note that many of these convergent miRNAs are synaptically enriched, suggesting that they may function at synaptic sites. Those miRNAs with a synaptic enrichment ratio (synaptic fraction/total homogenate) >2 are marked with a blue star (Lugli et al., 2008).

were associated with reduced miRNA expression levels (Moreau et al., 2011). Interestingly, when the 24 misexpressed miRNAs with posterior probabilities of a nonzero diagnostic effect >95% were compared with 22 identified in the mouse model of 22q11.2 microdeletion, 8 of them overlapped. Another line of evidence came from an expression profiling study of miRNAs in peripheral blood mononuclear cells of 112 patients with SCZ and 76 non-psychiatric controls (Gardiner et al., 2011). Gardiner et al. showed that a cluster of 17 of the most substantially downregulated miRNAs was located within an imprinted region (*DLK1-DIO3*) on chromosome 14 (14q32). These miRNAs account for 53% of the 30 miRNAs that lie within this locus and are expressed in the peripheral blood mononuclear cells (Gardiner et al., 2011). Notably, the expression levels of many miRNAs within this cluster including *miR-134* were also down-regulated in *Df(16)A*$^{+/-}$ and *Dgcr8*$^{+/-}$ mice. It is interesting to note that many of these convergent miRNAs have been suggested to be synaptically enriched (Lugli et al., 2008) (Fig. 1).

Although the observed fold change of individual miRNAs in studies of the *Df(16)A*$^{+/-}$ mouse model (Stark et al., 2008) as well as in human postmortem studies (Beveridge et al., 2008, 2010; Gardiner et al., 2011; Kim et al., 2010; Moreau et al., 2011; Perkins et al., 2007; Santarelli et al., 2011) is generally small, it is conceivable (although not yet unequivocally established) that even relatively small changes in specific miRNA levels can disrupt the regulation of the target protein expression. A recent study provided support to this notion by demonstrating that protein synthesis of a given target gene is nonlinearly sensitive to a threshold of its mRNA level, that is, protein production is severely repressed when its mRNA level is below the threshold and is proportion to the mRNA level when above the threshold. It is miRNAs that fine tune this threshold level of target mRNAs (Mukherji et al., 2011). Notably, many of the miRNAs found altered in the aforementioned expression profiling studies are not among the most highly expressed miRNAs in the brain, suggesting that instead of stoichiometrically saturating their target mRNAs under physiological conditions, they may "coexist" with them and fine tune their threshold levels. Transition of target mRNA levels around the threshold may be sensitive to even modest fluctuation in the levels of such miRNAs (especially for targets that have multiple binding sites for the dysregulated miRNAs) thus having considerable impact on target protein production. It has been recently shown that alterations in the levels of at least some miRNAs have a low magnitude but widespread impact on proteome, consistent with the notion that individual miRNAs can act as "rheostats" to adjust the fine-scale control of global protein output (Baek et al., 2008; Selbach et al., 2008). In that context, modest dysregulation of many miRNAs, which may interact additively or cooperatively, could, in principle, have an even more prevalent impact on proteome. Although more studies are required to examine if such effects are at play in individuals with 22q11.2 microdeletions, an alternative, but not mutually exclusive scenario is that 22q11.2 microdeletions, by partially disabling miRNA machinery, may act by creating a sensitized genetic background where the generally modest changes in the levels of a subset of miRNAs may act by unmasking additional deleterious mutations in these miRNA that affect their expression or activity but remain "dormant" in a wild type genetic background (Brenner et al., 2010).

Although targets of the Dgcr8-dependent miRNA dysregulation have not been reported yet, the functional consequences of alterations in miRNA biogenesis have been studied in some detail (Fig. 2). Behavioral tests showed that *Dgcr8*-deficient mice show impaired acquisition of the spatial working memory-dependent task (the T-maze delayed nonmatch to place task) as seen in *Df(16)A*$^{+/-}$ mice suggestive of altered function of the frontal regions of the mouse neocortex and/or their interaction with the hippocampus. Interestingly, unlike *Df(16)A*$^{+/-}$ mice, *Dgcr8*-deficient mice have normal associative memory. Thus, *Dgcr8* deficiency and the ensuing

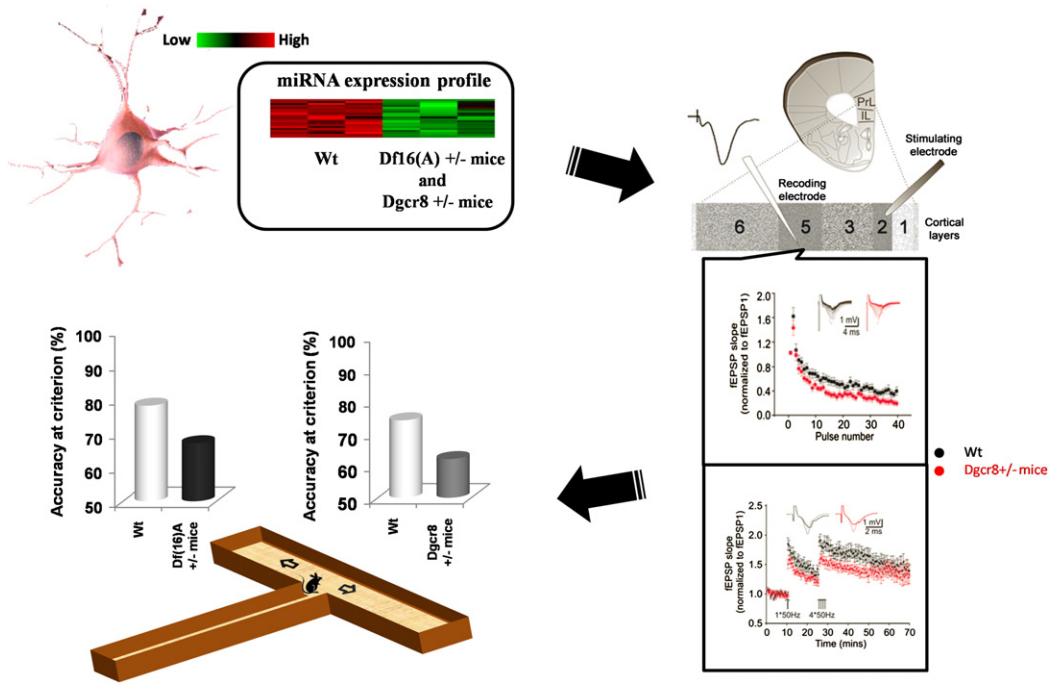

Fig. 2. Alterations in cognitive performance and synaptic plasticity due to 22q11.2 associated miRNA dysregulation. Both *Df(16)A*$^{+/-}$ and *Dgcr8*$^{+/-}$ mice show deficits in the T-maze delayed nonmatch to place task. Animals lacking a single copy of *Dgcr8* (*Dgcr8*$^{+/-}$ mice) show similar spatial WM deficits and offer a simpler genetic model for identifying at least some potential neural substrates. Interestingly, mPFC layer 5 neurons in *Dgcr8*$^{+/-}$ mutants show greater synaptic depression, less synaptic summation and reduced synaptic potentiation upon stimulation of their superficial afferents.

abnormality of miRNA biogenesis appears to contribute to some but not all of the cognitive phenotypes observed in the *Df(16)A*$^{+/-}$ mice. Pinpointing the affected miRNAs and their targets will facilitate the identification of the neural substrates underlying these phenotypes. Notably, cognitive deficits, in particular working memory deficits, have become increasingly recognized as key components of SCZ and may reflect a more general disruption of neural networks that underlie both sensory perception and cognition. Working memory is thought to be primarily modulated by the prefrontal cortex (PFC) and to depend on persistent and recurrent neuronal excitation even in the absence of continued sensory stimulation. In that respect, the cognitive profile of *Dgcr8* deficiency may reflect a bottom up impact from defects in neuronal connections and/or synaptic transmission or plasticity to cortical networks. Consistent with this notion, electrophysiology test on prefrontal pyramidal neurons of *Dgcr8*$^{+/-}$ mutant mice showed that layer 5 (L5) pyramidal neurons from heterozygous mutant mice showed a higher level of short-term synaptic depression (STD) and less potentiation following physiologically relevant persistent high-frequency stimulation, while intrinsic membrane properties and basal synaptic transmission upon activation of superficial layer afferents are normal. These synaptic phenotypes implicate a deficit at the presynaptic level in prefrontal pyramidal neurons of *Dgcr8*$^{+/-}$ mutant mice. On the contrary, unlike the robust deficits observed in the PFC basic synaptic transmission and plasticity at the CA3/CA1 synapse of *Dgcr8*$^{+/-}$ mice appeared normal suggesting that the effects of *Dgcr8* deficiency on synaptic plasticity are not manifested ubiquitously in the brain. *Dgcr8* deficiency caused only modest morphological changes in both PFC and hippocampus (Fenelon et al., 2011; Stark et al., 2008). These included changes in the density of layer 2/4 (L2/4) neurons, a modest but significant decrease in the size of spines of basal dendrites of cortical L5 and hippocampal CA1 pyramidal neurons as well as a modest decrease in the complexity of peripheral basal dendritic branches in CA1 pyramidal neurons. Using an independent *Dgcr8*$^{+/-}$ mouse model Schofield CM et al. showed that layer V pyramidal neurons in the medial prefrontal cortex of *Dgcr8*-deficient mice have decreased complexity of basal dendrites, and electrical properties were altered including decrease of frequency but not amplitude of miniature excitatory postsynaptic currents (mEPSC) and spontaneous excitatory postsynaptic Currents (sEPSC) of L5 pyramidal cells in slices from P25–30 mice (Schofield et al., 2011). The reason for the discrepancy between this and the Fenelon et al. study regarding basal excitatory transmission and dendritic structures is not clear. Nevertheless, both studies suggested the possible involvement of miRNA dysregulation in neuronal electrophysiological properties which warrants further investigation.

Recent human genetic studies have started providing suggestive evidence that the contribution of miRNAs and related processing enzymes to the genetic etiology of SCZ may extend beyond the 22q11.2 SCZ susceptibility locus. First of all, several large-scale genome-wide scans for structural variants associated with SCZ have identified a number of variants within the genes that control the miRNA biogenesis pathway. For example, Xu et al. identified a de novo duplication encompassing the *DICER1* gene in a genome-wide scan for de novo CNVs in sporadic SCZ (Xu et al., 2008a). *CYFIP1*, another gene within a recurrent CNV regions in a SCZ cohort on 15q11.2 (Stefansson et al., 2008), binds two components of miRNA mediated translational control machinery, the Fragile X Mental Retardation Protein (FMRP) and the translation initiation factor eIF4E (Jin et al., 2004; Napoli et al., 2008). In addition, genome-wide scans for CNVs have also identified a number of structural variants enriched in patients with SCZ that contain miRNAs. For example, *hsa-miR-211* and *hsa-miR-484* are within CNVs at 15q13.1 and 16p13.11 identified by several genome scans in SCZ samples (Ingason et al., 2011; ISC, 2008; Kirov et al., 2008, 2009; Stefansson et al., 2008). Furthermore, Hansen et al. conducted an association study of 101 brain expressed miRNA loci in a Danish and Norwegian SCZ cohort using a case–control design. They found suggestive evidence that two miRNA loci, *miR-206* and *miR-198* were associated with SCZ in the Danish and Norwegian sample, respectively (Hansen et al., 2007). More recently, a large sample genome-wide association study reported a strong association between SCZ and a genetic variant in the vicinity of the *miR-137* gene locus at chromosome 1p21.3 as well as weaker associations with a

number of predicted *miR-137* targets (Ripke et al., 2011). The effect of the linked variant on the expression of *miR-137* remains unknown and, provided that the reported association is not a false finding, it is expected to be rather modest. In addition, although supporting evidence for some of the predicted targets has been obtained using in vitro assays (Kwon et al., 2011) whether predicted targets represent genuine targets in vivo and more importantly whether they are responsive to the expected modest changes in *miR-137* expression remains to be determined. This is an important issue given the rather poor correct prediction rate of available programs (Rajewsky, 2006) and the fact that suppression of downstream targets is miRNA-concentration dependent (Mukherji et al., 2011). As we noted elsewhere (Rodriguez-Murillo et al., 2012) interpreting results from GWAS should be done with care and in the absence of a link between *miR-137* common variants and the function or expression of this miRNA the possibility that the positive correlation from GWAS reflect disease risk confered by a neighboring gene/locus cannot yet be excluded.

As mentioned above, miRNA expression-profiling studies have also observed significant changes in miRNA levels in postmortem brains of individuals with SCZ (Beveridge et al., 2008, 2010; Kim et al., 2010; Moreau et al., 2011; Perkins et al., 2007; Santarelli et al., 2011). In the first study of this kind, Perkins et al. studied the expression pattern of 264 human miRNAs using postmortem prefrontal cortex samples from 13 patients with SCZ and two with schizoaffective disorder, as well as 21 psychiatrically unaffected controls. They showed that fifteen miRNAs were significant decreased and one was upregulated in SCZ patients as compared with controls (Perkins et al., 2007). Although there are discrepancies among the various miRNA expression profiling studies, in aggregate and in the context of accumulating evidence from human genetic studies, they tend to support the view that altered miRNA levels could be a significant factor in the dysregulation of cortical gene expression in SCZ at least at the mRNA level. In the same context, the observations that the expression levels of some miRNAs are sensitive to antipsychotics or psychotomimetic drugs can also be interpreted as supportive (but not conclusive) evidence of involvement of miRNA related regulation in SCZ etiology. For instance, three miRNAs, *miR-128a*, *miR-128b* and *miR-199a* were up-regulated in response to haloperidol treatment in rats as compared to untreated controls (Perkins et al., 2007). In an independent study, *miR-219* expression level was reduced in the prefrontal cortex of mice in response to dizocilpine, a selective NMDA receptor antagonist. This dizocilpine-induced effect on *miR-219* could be attenuated by pretreating the mice with the antipsychotic drugs haloperidol and clozapine (Kocerha et al., 2009).

Autism spectrum disorders

Autism spectrum disorders (ASDs) are a heterogeneous group of neurodevelopmental disorders with impairment in social interaction and repetitive and stereotyped behaviors (as defined in DSM-IV, American Psychiatric Association, 1994). Symptoms start at age three or earlier. The prevalence of ASDs in general population is about 1%. Family and twins studies indicate a strong genetic component (Bailey et al., 1995; Folstein and Rutter, 1977; Greenberg et al., 2001; Steffenburg et al., 1989).

Several recent studies started to explore the possibility of whether dysregulation of miRNAs plays a role in ASDs. Several human genetic studies provided some potential connections between miRNA abnormalities and ASD phenotypes due to chromosome structural mutations. One such an example is the 22q11.2 microduplications. In contrast to the enrichment of 22q11.2 microdeletion (but not microduplication) in SCZ cohort (Brunet et al., 2008), a higher frequency of 22q11.2 microduplication (but not microdeletion) was observed in unrelated ASD cases according to the results of several genome-wide CNV screenings (Glessner et al., 2009; Marshall et al., 2008). Because the expression level of *DGCR8* gene is up-regulation in the 22q11.2 microduplication, miRNA biogenesis process is likely to be affected. In addition, *miR-185* gene within in the 22q11.2 duplication is also likely altered (BX, MK, JAG unpublished). Similarly, *hsa-miR-211*, another microRNA gene, is located within a recurrent genomic imbalance region at 15q13.2-q13.3 that has been associated with ASDs, intellectual disability, epilepsy, and/or electroencephalogram (EEG) abnormalities (Miller et al., 2009). A number of expression profiling studies examined miRNA dysregulation in ASD patient samples. Talebizadeh et al. checked the expression profile of 470 miRNAs of the lymphoblastoid cell line samples from 6 ASD patients and 6 matched controls using microarrays. Nine miRNAs were shown to be differential expressed in the ASD samples as compared to controls (Talebizadeh et al., 2008). In an independent study Abu-Elneel et al. probed the expression of 466 miRNAs of the postmortem cerebellar cortex samples from 13 ASD patients and 13 non-autistic controls using multiplex quantitative PCR method. They found that 28 out of 277 miRNAs that could be reliably detected were differentially expressed in at least one of the ASD samples as compared to the mean value observed in non-autistic controls (Abu-Elneel et al., 2008). Three miRNAs, *miR-23a*, *miR-134* and *miR-146b* overlapped between these two studies. More recently, Sarachana et al. compared miRNA expression in lymphoblastoid cells from three pairs of monozygotic twins discordant for diagnosis of ASD, a normal sibling for two of the twin pairs, two pairs of autistic and unaffected siblings, and a pair of normal monozygotic twins. 43 miRNAs were found as significantly changed between autistic and nonautistic individuals. Two miRNAs (*miR-23a* and *miR-106b*) overlapped with the ones reported by Abu-Elneel et al. (Abu-Elneel et al., 2008; Sarachana et al., 2010). Ghahramani Seno et al. used a discordant sibling pair design to study mRNA and miRNA expression profile in lymphoblastoid cells of 20 severe autism patients and 22 unaffected siblings. They identified a subgroup of samples with similar expression pattern using cluster analysis and determined that 12 miRNAs were differentially expressed in this subset of ASD samples (Ghahramani Seno et al., 2011). Although initial genetic studies at the genomic level suggest that miRNA alterations could contribute to the genetic heterogeneity and phenotypic variation of ASDs, miRNA gene profiling studies have not yet produced a convergent picture and additional larger scale systematic investigation will be necessary.

Rett syndrome

Rett syndrome (RTT) is a neurodevelopmental disorder with an incidence of 1:10,000–15,000 (Hagberg, 1985). RTT occurs almost exclusively in girls and 99% of affected girls are sporadic cases. Patients with classic RTT have an apparently normal development before 6–18 months of age, then gradually exhibit developmental stagnation, stereotypical movements, microcephaly, seizures, autistic features and intellectual disability (Hagberg et al., 1983). Detailed anatomic examination reveals that RTT patients have a smaller brain and the size and dendritic arborization of individual neurons are also reduced (Armstrong et al., 1995; Leonard and Bower, 1998; Sirianni et al., 1998).

Mutations in the gene encoding methyl-CpG binding protein 2 (*MeCP2*) have been associated with many RTT cases and are thought to be the main cause of RTT (Amir et al., 1999). Evidence that miRNAs might involve in the etiology and clinical expression of RTT came from the finding that *miR-132* controls the expression a *Mecp2* isoform in primary cortical neurons through its 3′UTR (Klein et al., 2007). This finding, combined with the observations that *miR-132* is a miRNA that regulates neuronal morphogenesis in responding to extrinsic trophic cues such as BDNF and that lack of *Mecp2* decreases BDNF levels in mouse models of RTT, suggested that *miR-132* might exert homeostatic control over *Mecp2* translation (Klein et al., 2007; Vo et al., 2005). More recently, Hansen et al. generated a transgenic

mouse strain where *miR-132* is over-expressed in forebrain neurons. *miR-132* transgenic mice displayed reduced Mecp2 levels, a significant increase of dendritic spine density in hippocampal neurons as well as deficits in a novel object test (Hansen et al., 2010). Interestingly, Mecp2 appears to also control miRNAs as well as their downstream targets. Nomura et al. (2008) reported that Mecp2 regulated the expression of another brain specific imprinted miRNA, miR-184, by binding to its promoter region. When cultured cortical neurons are depolarized, Mecp2 is released from the promoter binding site of the paternal allele leading to up-regulation of paternal allele-specific expression of miR-184. It should be noted, however, that the authors observed a down-regulation of miR-184 expression in the *Mecp2*-deficient mouse brain. In addition, no morphological consequence was identified when miR-184 was overexpressed in the cultured cortical neurons (Nomura et al., 2008). More recently, two miRNA expression profiling studies of a *Mecp2* knockout mouse model further demonstrated a broader alteration of miRNA expression in response to lack of *Mecp2*. Urdinguio et al. used miRNA microarrays to investigate the miRNA expression profiles of *Mecp2* knockout mice, a mouse model of Rett syndrome. They reported 65 out of 245 miRNAs altered in their expression with more than 70% of them downregulated (Urdinguio et al., 2010). Wu et al. used massively parallel sequencing methods to identify miRNAs altered in cerebella of *Mecp2*-null mice before and after the onset of severe neurological symptoms. They found that ~17% of all known mature miRNAs were considerably dysregulated (>1.5-fold) in cerebella of knockout mice before the onset of severe neurological symptoms. A further analysis revealed that many up-regulated mature miRNAs belong to the miRNA clusters within the Dlk1–Gtl2 imprinted domain (Wu et al., 2010). Interestingly, dysregulation of miRNAs within this genomic region was also reported in SCZ samples albeit in opposite direction (see Schizophrenia). Transcription of miRNAs within this cluster has been shown to be regulated by neuronal activity and has been implicated in regulation of dendritic morphology (Fiore et al., 2009). Overall, Mecp2 seems to be an important component of a miRNA-modulated regulatory network: miRNAs such as miR-132 control Mecp2 level and, in turn, Mecp2-regulated miRNAs may serve as critical mechanistic links to the downstream phenotypes. Therefore, deficits in *Mecp2* expression may lead to the disruption of miRNA regulatory machinery, which may contribute to clinical phenotypes observed in Rett syndrome.

Fragile X syndrome

Fragile X syndrome (FXS) is the most common inherited form of mental retardation, affecting about 1:4000 males and 1:8000 females (Turner et al., 1996). It results in a spectrum of cognitive and behavioral manifestation including deficits in speech and language skills similar to the ones seen in ASD patients (Merenstein et al., 1996). FXS is caused by the repeat expansion of a single trinucleotide gene sequence (CGG) in the 5′UTR of *FMRP*, which leads to the failure of *FMRP* gene expression (Penagarikano et al., 2007). FMRP is a RNA binding protein and is thought to act through its translational repression effect. It has been reported that mutations in FMRP affect neuronal morphology as well as electrophysiological properties of neurons such as synaptic plasticity and long term potentiation (Bolduc et al., 2008; Dictenberg et al., 2008; Huber et al., 2002; Jin et al., 2004; Zhang et al., 2001).

FMRP protein was found to associate with Argonaute-2 (Ago2) and Dicer, both of which are critical components of miRNA pathway (Caudy et al., 2002; Ishizuka et al., 2002; Jin et al., 2004). In addition, several studies indicated that the maturation and function of some miRNAs are partially FMRP dependent. Xu et al. showed that ectopic expression of *miR-124a* precursors in vivo decreased dendritic branching of sensory neurons in Drosophila. This effect was partially rescued by the inactivation of *dFMR1*. They further showed that pre-*miR-124a* (precursor of *miR-124a*) levels were increased while the level of the mature form was reduced in *dFMR1* mutants (Xu et al., 2008b). More recently, Edbauer et al. (2010) showed that several miRNAs, including *miR-125b* and *miR-132*, are associated with FMRP in the mouse brain. Alterations of *miR-125b* and *miR-132* expression resulted in spine morphology changes and FMRP was required for the effect of *miR-125b* and *miR-132* on the spine morphology. Furthermore, the expression of the NMDA receptor subunit *NR2A* was regulated by FMRP partially through *miR-125b* (Edbauer et al., 2010). This finding is consistent with the several previous results indicating that loss of *FMRP* alters NMDA receptor function in mice (Pfeiffer and Huber, 2007; Pilpel et al., 2009). Muddashetty et al. showed that *miR-125a* could reversibly control PSD-95 expression, which in turn, alters the dendritic spine morphology. FMRP phosphorylation status in response to mGluR signaling controls the binding affinity of AGO2-*miR-125a* complex to PSD-95 mRNA. These studies indicated that *FMRP* gene, at least in part, executes its function via miRNA-modulated regulatory networks.

Tourette's syndrome

Tourette's syndrome (TS) is a neurodevelopmental condition characterized by chronic vocal and motor tics and associated with behavioral abnormalities. TS has a prevalence of 1% in general population and 3/4 of the patients are male (Staley et al., 1997). The age of onset of the disease ranges from 2 to 14 years old with a peak age of tic onset at 6–7 years of age (Kerbeshian et al., 2009; Robinson, 2010). TS is often comorbid with other neuropsychiatric disorders such as attention deficit/hyperactivity disorder and obsessive–compulsive disorder (Cavanna et al., 2009). Although a strong genetic component is suggested based on family, segregation and twin studies, gene identification via linkage and association studies have been largely unsuccessful indicating it is a complex disease (O'Rourke et al., 2009).

A potential link between miRNA and TS was first proposed by Abelson et al. based on identification of a sequence variant (var321) in the 3′UTR of Slit and Trk-like1 (*SLITRK1*) gene (Abelson et al., 2005). The variant was identified when the authors screened the sequence surrounding the breakpoint of a de novo chromosomal inversion of a TS patient. Mutational screening of the resident *SLITRK1* gene in 174 unrelated TS patients revealed that two patients (but none of the 2148 controls) carried a sequence variant (var321) in the 3′UTR of *SLITRK1*, which affects the binding of a miRNA, *hsa-miR-189*. They further showed that *miR-189* has a modest dose-dependent effect on *SLITRK1* expression in an in vitro luciferase assay system. In situ hybridization experiments indicated that the expression of *miR-189* and *SLITRK1* mRNA is overlapping in many neuroanatomical circuits of postnatal mouse and fetal human brains that are most commonly implicated in TS (Abelson et al., 2005). Finally, over-expression of *SLITRK1* in cortical neuronal cultures was shown to promote dendritic growth (Abelson et al., 2005). The association between var321 variant and TS phenotype was followed up in several independent datasets (Chou et al., 2007; Deng et al., 2006; Keen-Kim et al., 2006; Scharf et al., 2008; Verkerk et al., 1991; Wendland et al., 2006; Zimprich et al., 2008). Although var321 was detected in some of these studies, it failed to cosegregate with TS phenotype. Because var321 is a very rare variant in the general population (minor allele frequency of 0.1%), additional studies with even larger samples in homogeneous populations are needed to clarify if the original finding was a false positive i.e. due to population stratification, a common problem with the case/control design or the follow-up replication studies was underpowered.

Down syndrome

The Down syndrome (DS) is characterized by mild to moderate mental retardation and its prevalence is estimated to be 1/800

(Carothers et al., 1999). The syndrome is caused by an extra whole or part of chromosome 21, which has a severe impact on the development of nervous system leading to impaired maturation of neurons including atrophic dendritic structure, decreased neuronal numbers and abnormal neuronal differentiation in the brain of DS patient. Some patients show early appearance of senile plaques (Mrak and Griffin, 2004; Wisniewski et al., 1985). A potential connection between miRNAs and DS phenotypes was recently explored (Kuhn et al., 2008). Five miRNA genes (*miR-99*a, let-7c, *miR-125b*-2, *miR-155*, and *miR-802*) located on human chromosome 21 were found up-regulated in the fetal brain tissue of DS patients compared to age- and sex-matched controls (Kuhn et al., 2008). The same group further demonstrated that a common target of *miR-155* and *miR-802* is Mecp2 (see Rett syndrome). In brain samples from human and mouse models, the expression of Mecp2 and its downstream targets, Creb1 and Mef2c, was all altered. In a DS mouse model, the expression level of Mecp2, Creb1 and Mef2c was restored when endogenous *miR-155* or *miR-802* was knocked down by intra-ventricular injections of corresponding antagomirs (Kuhn et al., 2010). These results suggest that over-expression of the miRNAs on chromosome 21 may repress the expression of *Mecp2*, which in turn contributes, at least in part, to the neural deficits observed in the brains of DS individuals. An important unresolved issue in these studies is that none of analyzed miRNAs are located within the Down syndrome critical region, which was previously identified to be associated with many of the DS phenotypes (Delabar et al., 1993). Therefore, how these miRNAs contribute to the DS phenotypes, especially intellectual disability requires further analysis.

Potential mechanistic connections between miRNA dysregulation and neuropsychiatric disorders

Although genetic and miRNA expression profiling studies described above provide strong evidence that miRNAs are involved in various psychiatric and neurodevelopmental disorders, the details on how miRNA dysregulation contributes to specific clinical pictures remains to be elucidated. A collective role of miRNAs in modulating normal neural morphology and function as well as various behavioral phenotypes is supported by many recent studies (see recent reviews in Fineberg et al., 2009; Siegel et al., 2011) and the impact of altered expression of individual miRNAs has been assessed using a variety of strategies. Below we discuss a few relevant examples that offer some potential mechanistic insight that might illuminate the connection between miRNA dysfunction and neuropsychiatric disorders.

Insights from global disruption of miRNA biogenesis and action

The majority of miRNAs identified so far are transcribed by RNA polymerase II as long primary transcripts called pri-miRNA. Pri-miRNAs are then processed into stem-loop precursor miRNAs (pre-miRNAs) by the microprocessor (a complex containing type-III RNase Drosha and its partner protein Dgcr8) in the nucleus. Pre-miRNAs are then exported to the cytoplasm and further cleaved into mature miRNA duplexes by Dicer, another type-III RNase. The final mature miRNAs have one strand incorporated into the ribosome induced silencing complex (RISC) with the help of Dicer and several other RNA binding proteins including Ago2, Pact and Trbp. The miRNA-associated RISC binds to the target mRNA to inhibit its translation or cause the degradation of the target mRNA (Kim, 2005). Disruptions of the components in miRNA biogenesis pathway have been shown to have a critical impact on neuronal survival, development, differentiation and function in the central nervous system. For example, knockout of the *Dicer* gene led to severe defects in neural tube morphogenesis arising from abnormal neuronal differentiation in zebra fish and embryonic lethal in mouse (Giraldez et al., 2005; Murchison et al., 2005). Conditional knockout of *Dicer* in mouse further demonstrated that morphogenesis of the neurons in the cortex and hippocampus was disrupted (Davis et al., 2008) and postnatal progressive neuron death observed in the cerebellum and forebrain (Kim et al., 2007; Schaefer et al., 2007). Mutation of *dAgo1*, one of the Argonaute proteins that facilitate the loading of miRNAs into the RISC, results in global developmental defects in Drosophila including the most prominent malformation of the nervous system (Kataoka et al., 2001). Similarly *Ago2*-null mice have severe defects in neural tube formation and die early in development (Liu et al., 2004). Deficiency of *Dgcr8* gene, which is disrupted by the 22q11.2 microdeletion, was the first example of a clinically relevant disruption of a component of miRNA biogenesis pathway. Similar to the situation of Dicer knockout, homozygous *Dgcr8* knockout mice die at embryonic day 6.5 (Stark et al., 2008; Wang et al., 2007), while *Dgcr8* heterozygous mice (*Dgcr8*+/−) show partially impaired miRNA biogenesis and result in a number of neuronal and behavioral deficits similar to what have been observed in human disease conditions (Fenelon et al., 2011; Schofield et al., 2011; Stark et al., 2008) (see Schizophrenia). Recently, the development of high throughput sequencing technologies and advanced bioinformatics tools, afforded the identification of many small RNAs with miRNA capabilities and characteristics. Interestingly, recent studies showed that these putative miRNAs are generated by bypassing one or more key steps of the classic pathway of miRNA biogenesis described above (Yang and Lai, 2011). It will be interesting to examine whether any components of these alternative pathways contribute to the various neuropsychiatric disorders.

Insights from disruption of individual miRNAs

Individual miRNAs modulate dendritic complexity and spine morphology in neurons

Alterations in dendritic complexity and spine morphology of neurons have been reported frequently in various psychiatric and neurodevelopmental disorders. Understanding the molecular underpinnings of these changes may provide insight into the etiologies of these conditions and may reveal new drug targets. *miR-134* is the first miRNA shown to contribute to dendritic complexity and spine morphology of neurons. Overexpression of *miR-134* significantly decreased spine volume while overexpression of a 2′-*O*-methylated anti-*miR-134* oligonucleotide increased spine width (Schratt et al., 2006). Schratt et al. proposed that BDNF treatment can relieve *miR-134*-dependent translation inhibition of its target, Limk1 (a kinase that regulates actin and microtubule polymerization), which in turn resulted in higher Limk1 protein level and dendritic spine morphology changes. Further investigation indicated that Myocyte enhancing factor 2 (Mef2) was necessary and sufficient to induce expression of *miR-134* in response to external stimuli, such as neurotrophic factors and neuronal activity. High level of *miR-134* inhibited translation of Pumilio2, a translational repressor and promoted neurite outgrowth (Fiore et al., 2009).

miR-132 is another extensively studied microRNA that has been shown to modulate neuronal morphology. Vo et al. identified *miR-132*, as a target of the transcription factor cAMP-response element binding protein (CREB) through a genome-wide screen. *miR-132* was enriched in neurons and tightly associated with a CREB element and was highly responsive to neurotrophin signaling. Overexpression of this miRNA in primary cortical neurons dramatically increased neurite outgrowth. Conversely, inhibition of *miR-132* blunted neurite outgrowth under basal conditions and blocked the response to BDNF (Vo et al., 2005). Magill et al. further demonstrated that ablation of the *miR-212/132* locus dramatically reduced dendritic length, branching, and spine density in newborn hippocampal neurons in young adult mice. Because *miR-132* was shown to be the predominantly active product of the *miR-212/132* locus in hippocampal neurons, the authors concluded that *miR-132* was required for normal dendrite maturation in newborn neurons in the adult hippocampus through

CREB mediated signaling (Magill et al., 2010). In an independent study, Hansen et al. employed a transgenic mouse strain that expresses *miR-132* in forebrain neurons. Morphometric analysis of hippocampal neurons indicated a dramatic increase in dendritic spine density in *miR-132* overexpressing mice (Hansen et al., 2010). Edbauer et al. further demonstrated that *miR-132* and *miR-125b* interacts with FMRP in mouse brain and regulated dendritic spine morphology of hippocampal neurons in opposite directions. Down-regulation of FMRP gene affected the impact of these miRNAs on spine morphology (Edbauer et al., 2010).

Overall, these studies suggest that a group of miRNAs plays multiple regulatory roles in controlling neuronal morphology in response to external stimuli, such as neurotrophic factors and neuronal activity. Given that *miR-134* is altered in the brain of the 22q11.2 microdeletion model (Stark et al., 2008) and alteration of *miR-132* expression is associated with FMRP expression (Edbauer et al., 2010), it would be tempting to speculate that the mechanisms suggested above might be part of the pathophysiological processes underlying the corresponding clinical conditions. Along these lines, observations from independent studies suggest that miRNAs may regulate dendritic morphology in concert with other disease-related signaling pathways. For example, two independent studies demonstrated that miR-138 controls the depalmitoylating enzyme lysophospholipase1 (Lypla1)/acyl protein thioesterase 1 (APT1), which modulates neuronal protein palmitoylation process (Banerjee et al., 2009; Siegel et al., 2009). In that respect, it is noteworthy, that in the case of the 22q11.2 microdeletion combined deficits of both miRNA biogenesis and neuronal palmitoylation (due to hemizygous deletion of *ZDHHC8* gene that encodes for a palmitoyltranferase) contribute to the changes in dendritic morphology and spine morphogenesis (Mukai et al., 2008; Stark et al., 2008).

Individual miRNAs modulate neurogenesis, neuronal proliferation, migration and integration

Neuropsychiatric disorders such as SCZ, ASD and mental retardation have been associated with a lot of neurodevelopmental abnormalities from neurogenesis, neuronal proliferation to neuron migration and integration (Hsieh and Eisch, 2010; Wegiel et al., 2010; Yang et al., 2011). Recent studies demonstrated that microRNAs take part in many aspects of these neurodevelopment processes. Therefore, the regulatory mechanisms involve in individual miRNAs might provide important insights of these pathogenic processes. *miR-124a* is one of the most abundant miRNAs in mammalian brain and mainly expressed in differentiating and mature neurons, accounting for 25%–48% of all mouse brain miRNAs (Deo et al., 2006; Lagos-Quintana et al., 2002). Ectopic expression of *miR-124a* in HeLa cells leads to a shift of expression profile from non-neuronal pattern to neuronal-like pattern (Lim et al., 2005) indicating that this miRNA might regulate the development of neuronal identity of the cells. Several studies have shown that *miR-124a* promote neuronal progenitor differentiation by de-repression of RE1-Silencing Transcription Factor (REST) and downregulation of target mRNAs such as PTBP1, a RNA-binding protein that globally represses alternative pre-mRNA splicing in non-neuronal cells (Conaco et al., 2006; Makeyev et al., 2007; Wu and Xie, 2006). More recently, Cheng et al. showed that *miR-124* regulated neurogenesis in the subventricular zone stem cell niche by repressing the SRY-box transcription factor Sox9 in the adult mammalian brain (Cheng et al., 2009). Yu et al. (2008) showed that *miR-124* controls neurite outgrowth in differentiating mouse P19 cells and mouse primary cortical neurons. In addition to it roles in neuronal development, Rajasethupathy et al. (2009) provided evidence that *miR-124* also plays an important role in serotonin mediated long-term plasticity of synapses in the mature nervous system of *Aplysia californica*.

miR-9 is another miRNA abundantly expressed in vertebrate brains (Griffiths-Jones, 2006; Lagos-Quintana et al., 2002). Several studies have suggested that *miR-9*/*miR-9** targets Nr2e1, REST, Corepressor of REST (CoREST), and BAF53a to suppress progenitor proliferation and promotes neural differentiation (Packer et al., 2008; Yoo et al., 2009; Zhao et al., 2009). *miR-9* also promotes proliferation of human embryonic stem cell-derived neural progenitors by targeting *STMN1* gene (Delaloy et al., 2010). Mutant mice lacking *miR-9-2* and *miR-9-3* (referred to as *miR-9-2/3* double mutants) designed to examine the *miR-9*/*miR-9** function in telencephalic development, exhibited dysregulation of pallial and subpallial progenitor proliferation/differentiation. They also exhibited multiple defects in telencephalic structures (Shibata et al., 2011).

Luikart et al. provided evidence that the expression pattern of *miR-132* is consistent with an effect on integration of newborn neurons in dentate gyrus into mature circuits. When a retroviral vector containing a "sponge" that consists of multiple *miR-132* binding sites was introduced into the newborn neurons and *miR-132* expression was down-regulated, the integration of newborn neurons into the excitatory synaptic circuitry of the adult brain was disrupted (Luikart et al., 2011). Interestingly, this mouse line also exhibited a decrease in the expression of MeCP2 and impairment in novel object recognition memory (Hansen et al., 2010). More recently, Gaughwin et al. showed that *miR-134* can modulate cortical development in a stage-specific fashion. Through interaction with Doublecortin and/or Chordin-like 1, *miR-134* promoted cell proliferation and counteracted Chrdl-1-induced apoptosis and Dcx-induced differentiation in neural progenitors. *miR-134* also affected neuronal migration in vitro and in vivo in a Dcx-dependent manner. When overexpressed in differentiating cortical neurons, *miR-134*, led to subtle alterations in neurites including reduction of number, length and overall complexity of processes. Exogenous BMP-4 treatment can significantly reverse the effect of *miR-134* overexpression. The author concluded that *miR-134* might be a modulator of exogenous BMP-4 signals on neurite outgrowth in a noggin-reversible manner (Gaughwin et al., 2011).

Individual miRNAs modulate neuronal electrophysiological properties in response to neuronal activity

miRNA expression is modulated by neuronal activity (Krol et al., 2010a) and studies from *Dgcr8* mutant mice have demonstrated that miRNAs alterations in neuropsychiatric diseases conditions lead to the changes of the electrical and synaptic properties of neurons (Fenelon et al., 2011; Schofield et al., 2011). Lambert et al. tested the effects of *miR-132* expression on synaptic function and their results indicated that the some properties in short term synaptic plasticity of cultured mouse hippocampal neurons were altered when *miR-132* was overexpressed including the increase of paired-pulse ratio and decreases synaptic depression. However, the presynaptic vesicular release properties such as the initial probability of neurotransmitter release, the size of the readily releasable pool of synaptic vesicles and the rate of refilling of vesicle pool were unchanged (Lambert et al., 2010). Therefore, the impact of individual miRNA expression on neuronal electrophysiological properties warrants further investigation.

Conclusions

The evidence reviewed here strongly suggests that miRNAs play an important role in the pathogenesis and pathophysiology of psychiatric and neurodevelopmental disorders as well as cognitive dysfunction. Although the exact mode of action of individual miRNAs affected in various psychiatric conditions remains largely unclear, our understanding is rapidly improving by the convergence of findings from various recent studies, including ones involving carefully designed animal models (Kvajo et al., 2011). A comprehensive understanding of the roles of miRNAs will be important for determining whether miRNAs-related pathways could serve as novel targets for drug development for these devastating conditions.

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