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Pathogenetic and therapeutic application of microRNAs in major depressive disorder

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Abstract

As a class of noncoding RNAs, microRNAs (miRNAs) regulate gene expression by inhibiting translation of messenger RNAs. These miRNAs have been shown to play a critical role in higher brain functioning and actively participate in synaptic plasticity. Pre-clinical evidence demonstrates that expression of miRNAs is differentially altered during stress. On the other hand, depressed individuals show marked changes in miRNA expression in brain. MiRNAs are also target of antidepressants and electroconvulsive therapy. Moreover, these miRNAs are present in circulating blood and can be easily detected. Profiling of miRNAs in blood plasma/serum provide evidence that determination of miRNAs in blood can be used as possible diagnostic and therapeutic tool. In this review article, these aspects are critically reviewed and role of miRNAs in possible etiopathogenesis and therapeutic implications in the context of major depressive disorder is discussed.

Keywords

miRNA; major depressive disorder; stress; circulating miRNAs; postmortem brain

Introduction

Major depressive disorder (MDD) is a common debilitating disorder with lifetime prevalence of more than 10% (Belmaker and Agam, 2008; Bromet et al., 2011). About 50% patients suffering from MDD show suicidal thought and tendency at some point in their lives; of them 10–15% eventually commit suicide (Möller, 2003). Interestingly, almost 50% of patients do not recover following an antidepressant trial and 20% of these patients fail to respond to any intervention (Warden et al., 2007; Labermaier et al., 2013). This is partially a result of poor understanding of the molecular pathophysiology underlying MDD.

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It is becoming increasingly evident that MDD may be associated with altered structural and synaptic plasticity, stress-related pathology, and to a certain extent, genetic polymorphism (Leistedt and Linkowski, 2013; Marsden, 2013; Ota and Duman, 2013). Disruptions across whole cellular networks and aberrant information processing in the circuits that regulate mood and cognition may lead to altered synaptic and structural plasticity and may be crucial in the development of MDD. In this context, microRNAs (miRNAs), a prominent class of small non-coding RNAs, have gained prominent attention for their role in neural plasticity and higher brain functioning and their possible role in neurodegenerative disorders as well as psychiatric illnesses. (Dwivedi et al., 2011; Im and Kenny, 2012; Garza-Manero, 2014; Hommers et al., 2015). By modulating translation and/or stability of a large number of mRNA targets in a coordinated and cohesive fashion, miRNAs have the capability to modulate disease phenotypes (Lages et al., 2012).

The miRNAs are encoded within primary miRNA gene transcripts (Bushati et al., 2007; Bartel et al., 2009). The primary miRNAs are transcribed by RNA polymerase II, which are then processed by Class 2 RNase III enzyme Drosha along with other co-factors to form one or a series of small hairpin miRNA precursors, known as precursor-miRNAs. These precursor miRNAs are ~70–110 nucleotides (nt) in length and fold into a stem-loop structure. The precursor-miRNAs are further processed in cytoplasm after being transported out of nucleus with the help of transportin 5 in conjunction with RanGTP. The stem loop structure is further processed by enzyme Dicer to form a double-stranded small RNAs about 22 nt. long. Generally, one of these strands is incorporated into a complex with one or more Argonaute homolog proteins (isoforms of eIF2c). The other strand is degraded (Krol et al., 2010). Thus, single-stranded mature miRNA, together with eIF2c and other associated proteins such as fragile X mental retardation protein (FMRP), comprises the so-called RISC complex. The RISC complex binds to specific “short seed” sequences located predominantly within the 3-untranslated region (UTR) region of mRNAs, and can interfere with translation of the mRNA and/or may reduce mRNA levels. In certain instances, miRNAs may activate translation or even act at the level of transcription by binding to specific gene promoters (Younger and Corey, 2011).

Although miRNAs have been extensively studied in neurodegenerative disorders, the research on miRNAs in MDD and other psychiatric illnesses are still in infancy. The evidence of the role of miRNAs in MDD is primarily derived from preclinical studies demonstrating the role of miRNAs in synaptic plasticity and neurogenesis. The other piece of evidence suggests that stress, a critical risk factor in MDD, differentially regulate miRNA-mediated expression of mRNA transcripts in rodent brain. In addition, postmortem brain studies in depressed individuals provide evidence that miRNAs may be involved in the etiopathogenesis of this disorder. More recently, miRNAs are being studied as diagnostic marker in psychiatric illnesses as miRNAs can be easily detected in serum/plasma. The aim of this review is to critically evaluate studies examining the role of miRNAs in MDD pathogenesis and whether miRNAs can be developed as diagnostic biomarker for MDD and antidepressant response.

miRNAs in Synaptic Plasticity

The role of miRNAs in synaptic plasticity has been extensively demonstrated by several investigators (Mercer et al., 2008; Costa-Mattioli, 2009; Bredy et al., 2011). Very recently, in an elegant review, Smalheiser (2014) has described the role of miRNAs at synapse and in learning and memory. Smalheiser laboratory has shown that primary miRNA gene transcripts are not all processed within the nucleus, instead, they are also expressed in cytoplasmic fractions enriched for RNA transport granules, where they are directly associated with KIF5 heavy chain, a motor protein used for dendritic RNA transport (Smalheiser, 2014). Additionally, they have shown that primary miRNAs are tightly associated with Drosha and DGCR8, the enzymes that process the primary miRNAs to precursor miRNAs. All of these components (primary miRNAs, Drosha and DGCR8) are enriched in purified synaptic fractions (synaptosomes and synaptoneurosomes) and postsynaptic densities (PSDs). This is true both for intronic and intergenic miRNAs (Lugli et al., 2008). These findings suggest that primary miRNAs are transported to synaptic regions in a manner similar to mRNAs and that miRNA biogenesis may occur locally near synapses in a regulated fashion. In another study by the same group, it was shown that Dicer and the RISC component eIF2c were expressed in the somatodendritic compartment of principal neurons and that Dicer was enriched in dendritic spines PSDs, suggesting a possible role of Dicer in synaptic plasticity (Lugli et al., 2010).

Several studies have shown the role of miRNA biogenesis enzymes in synaptic plasticity. For example, conditional Dicer knock out mice in excitatory forebrain neurons leads to reduced dendritic branch elaboration and large increase in dendritic spine length with no concomitant change in spine density (Schaefer et al., 2007; Davis et al., 2008). On the other hand, conditional Purkinje cell-specific ablation of Dicer caused Purkinje cell death (Schaefer et al., 2007). DGCR8 knockout mice show a loss of synaptic connectivity, reduced number and size of the dendritic spines (Stark et al., 2008; Olde Loohuis et al., 2012), and impaired spatial working memory-dependent tasks (Stark et al., 2008). Such memory deficits are often associated with depressive symptoms (Zaninotto et al., 2014). More recently, it has been shown that under conditions of elevated long-term potentiation (LTP) (Park and Tang, 2009; Lee et al., 2012) and long-term depression (LTD) in the hippocampal CA1 region lead to increased miRNA levels, which is associated with altered dendritic plasticity and synaptic transmission (Lee et al., 2012). FMRP, which regulates protein synthesis in dendritic spines after binding with specific sites within the 3’UTR of certain mRNAs in concert with RISC components Ago1 and Dicer, is also associated with learning, memory, and associated LTP (Ashraf et al., 2006).

Certain brain-specific individual miRNAs have been shown to regulate synaptic plasticity. Shratt et al. (2006) have shown that miR-134 is localized to the synapto-dendritic compartment of rat hippocampal neurons and negatively regulates the size of dendritic spines--postsynaptic sites of excitatory synaptic transmission. This effect is mediated by miR-134 inhibition of the translation of mRNA encoding a protein kinase, Lim kinase (Limk)1, involved in spine development. Exposure of neurons to brain-derived neurotrophic factor (BDNF) relieves miR-134 inhibition of Limk1 translation. miR-134 can also promote dendritogenesis by inhibiting translational repressor Pumilio2 (Fiore et al., 2009).

Interestingly, expression of *SIRT1* gene, which modulates synaptic plasticity and memory formation, is altered via posttranscriptional regulation of CREB by miR-134 (Gao et al., 2010). Conversely, *SIRT1* inhibits the expression of miR-134 via a repressor complex containing the transcription factor YY1. Unchecked miR-134 expression after *SIRT1* deficiency may result into the reduced expression of CREB and BDNF, whereas knocking down miR-134 rescues LTP and memory impairment caused by *SIRT1* deficiency (Gao et al., 2010). Both BDNF and CREB are implicated in MDD (Dwivedi et al., 2003a, 2003b).

MiR-132 has been studied the most with regards to synaptic plasticity. For example, miR-132 overexpresion increases dendritic protrusion as well as branching (Wayman et al., 2008). Neuronal activity rapidly induces transcription of the miR-132, in vivo (Nudelman et al., 2010). On the other hand, in vivo knockdown of hippocampal miR-132 expression impairs memory acquisition of trace fear conditioning (Wang et al., 2013). Interestingly, expression of miR-132 is induced by BDNF via CREB. On the other hand, CREB- and activity-regulated miR-132 is necessary for hippocampal spine formation (Impey et al., 2010). Expression of the miR-132 target, p250GAP, is inversely correlated with miR-132 and spinogenesis. Knockdown of p250GAP increases spine formation while introduction of a p250GAP mutant unresponsive to miR-132 attenuates this activity. Inhibition of miR132 decreases both mEPSC frequency and the number of GluR1-positive spines, while knockdown of p250GAP has the opposite effect (Impey et al., 2010).

Another miRNA, miR-124, plays a significant role in maintaining neuronal cell identity (Maiorano and Mallamaci, 2010). Interestingly, miR-124 is rapidly and robustly regulated by serotonin (5HT), which selectively affects mature miR-124 levels, without affecting its precursor, suggesting that the miR-124 level may be regulated during Dicer processing or RISC incorporation and stabilization by Ago (Rajasethupathy et al., 2009). MiR-124 responds to 5HT by de-repressing CREB and thereby enhances 5HT-dependent long-term facilitation (Rajasethupathy et al., 2009). Another miRNA, miR-125b targets NR2A gene and regulates synaptic plasticity in a negative fashion (Edbauer et al., 2010). Similar negative regulation of the size of dendritic spines in rat hippocampal neurons has been shown with miR-138 and miR-134. MiR-138 controls the expression of acyl protein thioesterase 1 (APT1), an enzyme regulating the palmitoylation status of proteins that are known to function at the synapse (Siegel et al., 2009). Dendritic morphology is also regulated by miR-9. Recently, using conditional inactivation of miR-9 approach in mouse brain, Giusti et al. (2014) demonstrated that miR-9 controls dendritic growth and synaptic transmission and downregulation of the transcriptional repressor REST is essential for proper dendritic growth.

Regulation of miRNAs by Stress: Possible Implications in Depressive Behavior

An individual's ability to cope with stress is critical in the development of depression. Recently we examined miRNA expression in frontal cortex of rats who developed behavior (learned helpless, LH) that resembles stress-induced depression and in at those who did not develop depression-like symptoms (non-learned helpless, NLH) despite similar exposure to inescapable shock (Smalheiser et al., 2011). We found that rats that did not develop

depression (NLH) showed a robust adaptive miRNA response to inescapable shocks whereas depressed (LH) rats showed a markedly blunted miRNA response. The miRNAs that were significantly altered were: miR-96, miR-141, miR-182, miR-183, miR-183*, miR-198, miR-200a, miR-200a*, miR-200b, miR-200b*, miR-200c, and miR-429. The *miRNAs denote the opposite arm of the precursor. These miRNAs were encoded at a few shared polycistronic loci, suggesting that their down regulation was coordinately controlled at the level of transcription. Interestingly, majority of these miRNAs have previously been shown to be enriched in synaptic fractions (Lugli et al., 2008). More interestingly, we identified a large core of co-expressed miRNAs hat were strongly correlated with each other across individuals of the LH group, but not in the NLH or tested control group. The presence of such a module implies that the normal homeostatic miRNA response to repeated inescapable shock is not merely absent or blunted in LH rats; rather, gene expression networks are actively reorganized in LH rats, which may support their distinctive persistent phenotype.

Using unpredictable chronic mild stress combined with separation, Cao et al. (2013) found changes in 13 specific miRNAs in rat hippocampus. These include: down-regulating miRNAs miR-298, miR-130b, miR-135a, miR-323, miR-503, miR-15b, miR-532, and miR-125a and up-regulating miRNAs miR7a, miR-212, miR-124, miR-139, and miR-182. Among these, miR-125a and miR-182 recovered to normal after intervention with antidepressant medication.

Differential regulation of miRNAs has also been reported in rat brain after acute and chronic restrained stress. In this study, Rinaldi et al. (2010) reported that acute stress induced expression of several miRNAs (miR-9, miR-9*, miR-26b, miR-29b, miR-30b, miR-30c, miR-30e, miR-125a, miR-126-3p, miR-129-3p, miR-207, miR-212, miR-351, miR-423, miR-487b, miR-494, miR-690, miR-691, miR-709, miR-711, and Let-7a-e) in frontal cortex. Interestingly, their expression levels are not altered after repeated restraint. These results suggest that acute stress modulates miRNA expression rapidly to external stimuli, which could be due to altered synaptic efficacy through regulation of localized mRNA translation. Interestingly, using chronic immobilization stress paradigms, Meerson et al. (2010) reported that acute and chronic immobilization stress differentially altered the expression of miRNAs in two stress-responsive regions of the rat brain, the hippocampal CA1 region and the central nucleus of the amygdala. MiR-134 and miR-183 levels both increased in the amygdala following acute stress, compared to unstressed controls. Chronic stress decreased miR-134 levels, whereas miR-183 remained unchanged in both the amygdala and CA1. Importantly, miR-134 and miR-183 shared a common predicted mRNA target, encoding the splicing factor SC35, a gene that promotes the alternative splicing of acetylcholinesterase (AChE) from the synapse-associated isoform AChE-S to the, normally rare, soluble AChE-R protein. One of the targets of miR-183 is profilin 2 mRNA, which regulates dendritic spine morphology in neurons. Interestingly, neurotransmitter homeostasis and behavior are severely affected in profilin 2 knockdown mice (Witke, 2004) and profilin 2 expression is increased in lymphoblastoid cell lines of monozygotic twin pairs discordant for bipolar disorder (Matigian et al., 2007). In another study, Zhang et al. (2013) examined the effect of maternal deprivation and chronic unpredictable stress in inducing depressive behaviors and associated molecular mechanism in rats. They found higher miR-504 expression and lower

dopamine receptor (DR) D1 and D2 expression in the nucleus accumbens of rats under both conditions. MiR-504 expression correlated negatively with DRD1 gene expression and sucrose preference rate but correlated positively with immobility time in forced swim test. Both DRD2 mRNA and protein expression correlated negatively with immobility time in forced swim test. These results suggest that maternal deprivation enhances behavioral vulnerability to stress during adulthood, which is associated with the upregulation of miR-504 and downregulation of DRD2 expression in the nucleus accumbens. Under chronic unpredictable stress, Bai et al. (2014) reported that anhedonia in rat is associated with upregulation of Let-7a and downregulation of Htr4 expression in the hippocampus. Earlier, Bai et al. (2012) reported that depression induced by maternal deprivation but not chronic unpredictable stress was significantly associated with upregulation of miR-16 and subsequent downregulation of BDNF gene in hippocampus.

Recently, the role of miRNAs in regulating serotonergic neuronal activity was explored by Issler et al. (2014). They identified a strong miRNA-target interaction between miR-135 and 5HT transporter and 5HT receptor-1a transcripts. Intriguingly, miR-135a levels were upregulated after administration of antidepressants. Genetically modified mouse models, expressing higher or lower levels of miR-135, demonstrated major alterations in anxiety- and depression-like behaviors, 5HT levels, and behavioral response to antidepressant treatment. They also found that miR-135a levels in blood and brain of depressed patients were significantly lower. These results suggest a potential role for miR-135 in MDD and this miRNA may act as an endogenous antidepressant (Issler et al, 2014).

Interestingly, Rodgers et al. (2013) reported that paternal stress exposure can alter sperm miRNA content and reprogram offspring HPA stress axis regulation. This could have potential impact in the development of MDD and other stress-related disorders transmitted via epigenetic regulation of miRNAs. In this context, it has earlier been reported that glucocorticoid receptor (GR) protein is under constant regulation by miRNAs (Vreugdenhil et al., 2009); specifically, via miR-124a and miR-18a (Vreugdenhil et al., 2009). Overexpression of miR-18a attenuates glucocorticoid-induced leucine zipper, a gene induced by stress-like levels of glucocorticoid. Interestingly, Uchida et al (2008) found that miR-18a-mediated down-regulation of GR translation is important in susceptibility to stress.

As mentioned earlier, Dicer knock out mice show altered synaptic plasticity. Haramati et al. (2013) recently found that Dicer ablation in central amygdala induced a robust increase in anxiety-like behavior in mice. Acute stress in wild-type mice induced a differential expression profile of miRNAs in the amygdala. One of the prominent stress-induced miRNAs identified was miR-34c, which was upregulated after acute and chronic stressful challenges and downregulated in Dicer ablated cells. Overexpression of miR34c within the adult central amygdala induced anxiolytic behavior. One of the identified miR-34c targets genes was corticotropin releasing factor receptor type 1 (CRFR1). MiR-34c reduced the responsiveness of cells to CRF in neuronal cells endogenously expressing CRFR1. In basolateral amygdala of mice, Volk et al. (2014) recently showed that miR-19b is modulated in response to social-defeat stress, which was associated with altered expression of adrenergic receptor β-1. Bilaterally injection with miR-19b into the this brain area showed lower freezing time relative to control in the cue fear conditioning test, and caused

deregulation of noradrenergic circuits mediated through adrenergic receptor β-1. This study suggests that that miR-19b play a key role in modulating behavioral responses to chronic stress and adrenergic receptor β-1 as an important target of miR-19b in stress-linked brain regions.

Very recently, Dias et al. (2014) have shown that β-catenin, a gene implicated in depression, mediates pro-resilient and anxiolytic effects in the nucleus accumbens in mice. Using genome-wide β-catenin enrichment mapping, they found that β-catenin acts as a critical regulator in the development of behavioral resilience by activating a network that includes Dicer1 and downstream miRNAs.

Human Postmortem Brain Studies of miRNAs: Direct Evidence Demonstrating the Role of miRNAs in MDD

Our group was the first to examine global expression of miRNAs in dorsolateral prefrontal cortex (dlPFC) of depressed suicide subjects (Smalheiser et al., 2012). We reported significant dounregulation of 21 miRNA in depressed subjects; many of them have been implicated in cellular growth and differentiation and some of them showed high synaptic enrichment (Lugli et al., 2008). These miRNAs arose from both intronic and intergenic loci. An additional 16 miRNAs were decreased by 30% or more that failed to meet the criterion for significance. Almost half of the combined down-regulated miRNAs were encoded at chromosomal loci near another miRNA on the list and were transcribed by the same primary miRNA gene transcripts. In addition, three pairs of miRNAs were encoded at distances greater than 100 kb but still lied within the same chromosomal region: a) mir-424 and 20b at Xq26.2-3, 377 kb apart; b) mir-142 and 301a at 17q22, 820 kb apart; and c) mir-324-5p and 497 at 17p13.1, 205 kb apart. Many of the downregulated miRNAs also shared 5′-seed sequences that were involved in target recognition. For example, identical seed sequences were shared by a) mir-20a and 20b; b) mir-301a and 130a; and c) mir-424 and 497. As well, a 6-mer nucleotide motif was shared by mir-34a, 34b* and 34c, and strikingly, a 5-mer motif (AGUGC) within the 5′-seed was shared by 5 of the affected miRNAs (mir-148b, 301a, 130a, 20a, 20b) that was predicted to bind Alu sequences within the 3′-UTR region of target mRNAs. This suggested that the down-regulated miRNAs should exhibit extensive overlap among their mRNA targets.

When pair-wise correlations were made, a set of 29 miRNAs were identified, none of which were pair-wise correlated in the normal control group, but which formed a very extensive inter-connected network in the depressed group. Target analysis revealed that many of the targets were transcription factors, and nuclear, transmembrane and signaling proteins. Intriguingly, 4 different down-regulated miRNAs targeted VEGFA (miR-20b, 20a, 34a, 34b*), a molecule implicated in depression in both humans and in animal models. Other validated targets include BCL2 (miR-34a), DNMT3B (miR-148b), and MYCN (miR-101, 34a). Among predicted targets, estrogen receptor alpha, ESR1, was predicted to be targeted by 3 different down-regulated miRNAs (miR-148b, 301a, 496). Others targeted by 3 or more affected miRNAs include ubiquitin ligases (UBE2D1 and UBE2W), signal transduction mediators (CAMK2G, AKAP1), the splicing factor NOVA1 that regulates brain-specific alternative splicing; the GABA-A receptor sub-unit GABRA4; calcium

channel CACNA1C; and brain-active transcription factors including SMAD5, MITF, BACH2, MYCN, and ARID4A. Several of these predicted targets interacted with validated targets; for example, ARIA4A binds E2F1; SMAD5 binds RUNX1; and estradiol treatment decreases E2F1 levels in prefrontal cortex (Wang et al., 2004). BACH2 transcription factor binding sites have been identified upstream of many brain-expressed miRNAs (Wu and Xie, 2006). Retinoblastoma binding protein 1 (ARIA4A) is of interest because it recruits histone deacetylases and regulates gene expression via chromatin-based silencing.

Selected target proteins such as DMNT3b, VEGFA, and BCL2 were studied by examining their expression in depressed suicide brain. DMNT3b was strongly up-regulated in the depressed suicide group, whereas BCL2 was downregulated. Several miRNAs that were co-regulated with their targets showed a strong positive correlation with DMNT3b and BCL2. A variety of factors such as transcription factor activity and turnover rate, as well as possible regulatory effects of other miRNAs may also be responsible for changes in mean expression levels of these target proteins. In addition, DNMT3b levels showed an extremely strong positive correlation with miR-148b across subjects. Similarly, BCL2 was strongly and positively correlated with miR-34a in the depressed suicide group. The correlation of miR-34a was positive in healthy controls, but inverse in the depressed suicide group, presumably reflecting a reorganization of miRNA-target networks (Smalheiser et al., 2012).

A previous study indicates that TrkB-T1, a BDNF receptor lacking a tyrosine kinase domain that is highly expressed in astrocytes and regulates BDNF-evoked calcium transients, is downregulated in frontal cortex of suicide subjects (Ernst et al., 2009). In a recent study, Maussion et al (2012) examined whether TrkB-T1 gene is regulated by miRNAs. Using postmortem brain samples obtained suicide subjects (60% were depressed) these investigators found that miR-185* and miR-491-3p were upregulated in subjects who showed low expression of TrkB.T1. Bioinformatic analyses revealed five putative binding sites for the DiGeorge syndrome linked miR-185* in the 3'UTR of TrkB-T1, but none for miR-491-3P. These results suggest that an increase of hsa-miR-185* expression levels regulates, at least in part, the TrkB-T1 decrease observed in the frontal cortex of suicide subjects.

Since polyamine system has been reported to play a role in predisposition to suicidal behavior (Fiori et al., 2011), Lopez et al. (2014a) examined whether dysregulation of polyamine genes in depressed suicide subjects could be influenced by miRNA post-transcriptional regulation. They identified several miRNAs that target the 3'UTR of polyamine genes SAT1 and SMOX. When the expression of 10 miRNAs in the prefrontal cortex of suicide subjects and controls were profiled, they found that several miR-139-5p, miR-320c were inversely correlated with SAT1 whereas miR34c-5p and miR-320c were inversely correlated with SMOX. These results suggest a relationship between miRNAs and polyamine gene expression in suicide brain, and postulate a mechanism for SAT1 and SMOX down-regulation by post-transcriptional activity of miRNAs.

More recently, Lopez et al. (2014b) reported that miR-1202, a miRNA specific to primates and enriched in the human brain, was differentially expressed in individuals with depression.

Additionally, miR-1202 regulated expression of the gene encoding metabotropic glutamate receptor-4 (GRM4) and predicted antidepressant response at baseline.

Genetic Susceptibility and miRNAs: Role in Depression

Given that MDD has heritability rate of ~40% (Sullivan, 2000), it is interesting to examine whether there are any genetic variations or polymorphisms in miRNAs or genes responsible for synthesis of miRNA processing in MDD patients. Jensen et al. (2009) for the first time identified an element (A-element) within 5HT receptor 1B (HTR1B) gene, which was negatively regulated by miR-96. The repressive activity A-element was attenuated by a common human variant (G-element) that disrupted a nucleotide important for its interaction with miR-96. This finding is important as HTR1B has been implicated in aggression and serve as a critical endophenotype in suicidal behavior (Bortolato et al., 2013). In addition, individuals homozygous for the ancestral A-element show more conduct-disorder behavior than individuals with the G-element, suggesting that such functional variants may be involved in complex behavioral disorders (Jensen et al., 2009).

Saus et al. (2010) studied whether naturally occurring variations in the sequences of miR-132, miR-219-1 or the miR-183/96/182 cluster, which act as modulators of the endogenous clocks, or changes in their target binding sites in the *RFX4, PHLPP, ADCY6* and *CLOCK* genes known to be involved in circadian clock period could be related to a higher susceptibility to MDD. They found a significant association between the T allele of the rs76481776 polymorphism in the pre-miR-182 and late insomnia in MDD patients. In addition, a significant overexpression of miR-182 was detected in cells transfected with the mutated pre-miR-182. Moreover, a significant reduction in luciferase activity of plasmids with 3' UTR of ADCY6, CLOCK and DSIP genes was shown when transfected with the mutated form of pre-miR-182. These data indicate that abnormal processing of pre-miR-182 in patients carrying the T allele of the rs76481776 polymorphism may contribute to the dysregulation of circadian rhythms in MDD patients with insomnia, which could influence expression levels of the mature form of miR-182 and might increase downregulation in some of its target genes.

Xu et al. (2010) detected a statistically significant positive association between miR-30e ss178077483 and MDD. Moreover, the P300 latency in MDD patients was associated with miR-30e ss178077483 genotypes and the individuals with the C/T genotype had a longer P300 latency than those carrying the C/C genotype, suggesting that polymorphisms in miR-30e may play an important role in MDD susceptibility. He et al. (2012) studied *g*enetic variations in miRNA processing genes and their association with susceptibility to MDD. Frequencies of genotypes and alleles showed significant difference between patients with MDD and healthy controls in DGCR8 rs3757 and AGO1 rs636832. An allele frequency was significantly higher in rs3757 and lower in rs636832, respectively. Variant allele of DGCR8 rs3757 was associated with increased risk of suicidal tendency and improvement response to antidepressant treatment, whereas the variant of AGO1 rs636832 showed decreased risk of suicidal tendency, suicidal behavior, and recurrence. Besides, allele frequency showed significant difference when compared patients with remission to controls, no significant differences were found in GEMIN4 rs7813 between patients and healthy controls. DGCR8

rs3757 and AGO1 rs636832 were found to have significant association with MDD, and GEMIN4 rs7813 did not affect susceptibility to MDD. These observations suggested that miRNA processing polymorphisms may affect MDD risk and treatment response.

Blood Cell miRNAs: A Valuable Source for Biomarker Discovery in MDD

There have been several reports which show that miRNAs can be detected in body fluids such as blood and CSF (Chen et al., 2008; Cogswell et al., 2008; Hunter et al., 2008; Weber et al., 2010; Baraniskin et al., 2012). These miRNAs show unexpected stability (Chen et al., 2008; Mitchell et al., 2008). Because of these reasons, there is a tremendous interest in the use of peripheral miRNAs for translational research in a variety of disease pathophysiology, including neuropsychiatric diseases (Rao et al., 2013; Maffioletti et al., 2014). Interestingly, under healthy conditions, these miRNAs are stably expressed; however, under pathological conditions, the profile of miRNAs changes tremendously (Jin et al., 2013). In addition, the changes in expression of miRNAs in blood cells correlate with changes in neuronal tissue. For example, a significant correlation between changes in blood and brain miRNAs has been reported for Alzheimer's disease, Huntington's disease, ischemic, and traumatic brain injuries (Redell et al., 2010; Liu et al., 2010; Gaughwin et al., 2011). Because of heterogeneity and complex nature of psychiatric illnesses, identifying biomarker in these diseases has been a challenging task. Nonetheless, emerging studies provide evidence that blood miRNAs can be used successfully as biomarker in these illnesses. The use of miRNAs as peripheral biomarker in depression is gaining momentum. For example, Belzeaux et al. (2012) found changes in several miRNAs (has-miR-107, miR-133a, miR-148a, miR-200c, miR-381, miR-425-3p, miR-494, miR-517b, miR-579, miR-589, miR-636, miR-652, miR-941, miR-1243) in peripheral blood mononuclear cells of severely MDD patients compared with healthy controls. Of them 2 miRNAs showed stable overexpression in MDD patients after 8-week follow-up (miR-941 and miR-589). Based on miRNA and predicted mRNA profiling, they identified a combination of four genes (PPT1, TNF, IL1B and HIST1H1E) that could have predictive value of treatment response.

Because of the critical role of BNDF in MDD pathophysiology (Dwivedi et al., 2009), expression of BDNF and miRNAs that target BDNF gene have been studied in serum of MDD patients. Li et al., (2013) found that two putative BDNF associated miRNAs, miR-182 and miR-132 were upregulated along with decreased levels of BDNF in MDD patients and that there was a significant negative correlation between the Self-Rating Depression Scale score and serum BDNF levels, and a positive correlation between the Self-Rating Depression Scale score and miR-132 levels.

Bocchio-Chiavetto et al. (2013) conducted a whole-miRNome analysis in the blood of 10 MDD patients after 12 weeks of treatment with escitalopram. They found that 30 miRNAs were differentially expressed after the escitalopram treatment: 28 miRNAs were up-regulated, and 2 miRNAs were downregulated. Among the differentially regulated miRNAs, miR-132 has been implicated in neurogenesis and synaptic plasticity, whereas miR-26a, miR-26b and miR-183 contributes to the action BDNF in brain (Wayman et al., 2008; Kawashima et al., 2010; Caputo et al., 2011). MiR-132, miR-26a, miR-26b, miR-183, let-7d, let-7e, miR-26b, miR-103, miR-128, miR-494 and miR-22 have been reported to play

a role in the pathogenesis of psychiatric disorders and in the mechanism of action of antipsychotic drugs and mood stabilizers. On the other hand, miR-494 and miR-335 have been shown to be down-regulated in the prefrontal cortex of depressed suicide patients (Smalheiser et al., 2012).

More recently, Fan et al. (2014) profiled miRNAs in peripheral blood mononuclear cells of 81 MDD patients and 46 healthy controls. They found that the expression levels of 5 miRNAs (miRNA-26b, miRNA-1972, miRNA-4485, miRNA-4498, and miRNA-4743) were up-regulated. MiRNA target gene prediction and functional annotation analysis showed that there was a significant enrichment in several pathways associated with nervous system and brain functions, supporting the hypothesis that differentially-regulated miRNAs may be involved in mechanism underlying development of MDD.

Can miRNAs Severe as Therapeutic Targets and in the Development of Target Based Therapy

Although not studied in greater detail, there are some studies which suggest that mechanisms of action of antidepressants could be associated with changes in miRNA expression and function. Since selective 5HT reuptake inhibitors (SSRIs) reduce 5HT transporter (SERT) expression at translational but not at the transcriptional level (Benmansour et al., 2002), the role of miRNAs were examined in the regulation of SERT expression. It was found that miR-16 has inverse correlation with SERT expression (Baudry et al., 2010; Hansen and Obrietan, 2013). Interestingly, treatment of mice with fluoxetine elevates the levels of miR-16 in serotonergic raphe nuclei and reduces SERT expression (Launay et al., 2011). Furthermore, the fluoxetine-mediated increase in miR-16 level in raphe is accompanied by a decrease in pre/pri–miR-16 supporting the hypothesis that fluoxetine-induced up-regulation of miR-16 in raphe nuclei involves enhanced maturation from pre/pri-miR-16. Surprisingly, fluoxetine decreases the level of miR-16 in the noradrenergic locus coeruleus, which is associated with the action of neurotrophic protein S100β released by raphe in response to fluoxetine treatment (Launay et al., 2011). Putative miRNA binding sites in human SERT 3’UTR have also been predicted by bioinformatics analysis and validated by leuciferase reporter assay experiments (Moya et al., 2012). The data obtained from those reporter assay experiments indicates that not only miR-16 but miR-15a also plays a role in regulation of SERT expression in raphe nuclei.

In rat model of electroconvulsive therapy (ECT), Ryan et al. (2013) examined expression of BDNF-associated miRNAs in rat brain and blood following acute or chronic (x10) ECS treatment. They found that level of one of the BDNF-related miRNAs miR-212 was significantly increased in rat dentate gyrus following both acute and chronic ECS. MiR-212 level was also increased in blood following chronic ECS and this was positively correlated with miR-212 level in the dentate gyrus. These results suggest that alterations in miR-212 may be associated with BDNF modulation by ECS and that altered miR-212 expression in both blood and brain can be used as an indicator of ECS response.

In a PTSD mouse model, Schmidt et al. (2013) assessed miRNA profiles in PFC dissected from either fluoxetine or control-treated wild-type C57BL/6N mice 74 days after their

subjection to either a single traumatic electric foot-shock or mock-treatment. Of 5 putative altered miRNAs under shock conditions, they found that therapeutic action of fluoxetine was associated with a significant reduction in mmu-miR-1971 expression, suggesting that traumatic stress and fluoxetine interact to cause distinct alterations in the mouse PFC miRNA.

Enoxacin, an antibacterial fluoroquinolone compound, stabilizes TRBP-Dicer complex. Recently, we showed that treatment of rats with enoxacin for one week increased the expression of miRNAs in frontal cortex and decreased the proportion of rats exhibiting learned helpless behavior following inescapable shock, suggesting that enoxacin may ameliorate depressive behavior, possibly due to upregulation of miRNAs (Smalheiser et al., 2014).

From these and a few previously mentioned antidepressant treatment studies in MDD patients, it appears that miRNAs are targets of a variety of therapeutic agents. Based on these studies, can miRNAs be used as a target to develop new therapeutic agents is an open question? Interestingly, in cancer biology, several therapeutic approaches have been used either to reduce or overexpress miRNA that have been shown to be directly associated with proliferation. For example, miRNA oligonucleotides have been generated, which can directly compete with endogenous miRNAs. This strategy has been successfully in targeting specific miRNA (eg., miR-21) and reducing its expression, which otherwise is overexpressed in several types of cancer (Si et al., 2007). The other strategy to reduce miRNA expression is to employ locked-nucleic-acid antisense oligonucleotides, which requires a sequence with perfect complementarity to the target gene such that duplexing can occur with higher affinity than that between the target gene and its endogenous miRNA (Ebert et al., 2007). miRNAs can also be overexpressed. For this, adenovirus-associated virus containing specific miRNAs can be delivered to the target tissue (Kota et al., 2009). In addition, miRNA mimics can be used to increase specific miRNA expression. These double-stranded RNA molecules mimic endogenous mature miRNAs (Landen et al., 2005). Thus, there are many strategies that can be used to inhibit or overexpress miRNA of interest. Several of these strategies are in pipeline for neurodegenerative diseases (Meng et al., 2013) but it will be interesting to see if these methods/strategies are useful in the complex disorders such as MDD.

Conclusion and Future Perspectives

As discussed above, both direct and indirect evidence suggest that miRNAs may participate in the etiopathogenesis of MDD. However, there are several limitations to these studies; one being the heterogenic nature of MDD. Before making any conclusive determinations, various clinical sub-phenotypes and confounding variables need to be carefully considered. For example, it will be interesting to examine whether changes in miRNAs are similar or dissimilar in melancholic vs. non-melancholic MDD patients. There is a genetic susceptibility to depression. As mentioned earlier, SNPs and genetic variants have been determined in certain miRNAs in MDD patients. However, more studies in a large number of patients are required to confirm these findings. Besides genetic, epigenetic regulation of

miRNAs has been proposed. Several miRNAs possess CpG binding sites within the promoter regions, which can potentially be regulated via methylation.

As has been discussed earlier, presence of miRNAs biogenesis machinery in the synapse may regulate gene expression locally. Since MDD is associated with altered synaptic plasticity, it will be interesting to examine whether miRNAs are synthesized at the and whether these miRNAs regulate synaptic proteins involved in MDD pathogenesis.

The presence of miRNAs in peripheral tissues, particularly, in blood cells provide promising approach to use miRNAs as potential biomarkers for both diagnosis and treatment response. However, there are several issues that need consideration for the use of circulating miRNAs as biomarkers. For example, the source of miRNAs in blood cells is not clear at the present time. In this regard, profiling exosomal miRNAs derived from brain may prove useful. The actively secreted miRNAs are enclosed in exosomes, which can cross blood-brain barrier (Alvarez-Erviti, 2011; Lakhal and Wood, 2011; Vickers et al., 2011;) and are well protected from degradation (Keller et al., 2011; Cheng et al., 2014). Exosomal miRNAs are processed by the same machinery used in miRNA biogenesis and thus have widespread consequences within the cell by inhibiting the expression of target protein-coding genes. Evidence showing that exosomal miRNAs are excreted physiologically in response to stress, lend the credence that exosomal miRNAs can be ideally used as potential biomarker candidate (Mendell, 2012).

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Table 1

MiRNAs implicated in Stress and MDD

miRNAs	Effects	References
Restraint stress	Frontal cortex: miR-9, miR-9*, miR-26b, miR-29b, miR-30b, miR-30c, miR-30e, miR-125a, miR-126-3p, miR-129-3p, miR-207, miR-212, miR-351, miR-423, miR-487b, miR-494, miR-690, miR-691, miR-709, miR-711, and Let-7 a–e let-7a, miR-9, miR-26a/b, miR-30b/c, and miR-125a	Rinaldi et al., 2010
Immobilization stress	Hippocampus CA1, amygdala: miR-134, miR-183, miR-132, Let-7a-1, miR-9-1, and miR-124a-1	Meerson et al., 2010
Unpredictable chronic mild stress	Hippocampus: miR298, miR-130b, miR-135a, miR-323, miR-503, miR-15b, miR-532, and miR-125a and up-regulating miRNAs miR7a, miR-212, miR-124, miR-139, and miR-182	Cao et al., 2013
Early life stress	Medial prefrontal cortex: pre-miRs 132, 124-1, 9-1, 9-3, 212, and 29a	Uchida et al., 2013
Animal model of depression	Learned helpless vs. Control frontal cortex: mmu-miR-184, mmu-miR-197, mmu-miR-107, mmu-miR-329, mmu-miR-125a-5p, mmu-miR-872, mmu-miR-181c, mmu-miR-18a*, mmu-miR-29b*, mmu-let-7a*, rno-let-7e*, rno-miR-20a*	Smalheiser et al., 2011
Postmortem brain studies	Prefrontal cortex: hsa-miR-142-5p, hsa-miR-33a, hsa-miR-137, hsa-miR-489, hsa-miR-148b, hsa-miR-101, hsa-miR-324-5p, hsa-miR-301a, hsa-miR-146a, hsa-miR-335, hsa-miR-494, hsa-miR-20b, hsa-miR-376a*, hsa-miR-190, hsa-miR-155, hsa-miR-660, hsa-miR-552, hsa-miR-453, hsa-miR-130a, hsa-miR-27a, hsa-miR-497, hsa-miR-10a, hsa-miR-20a, hsa-miR-142-3p	Smalheiser et al., 2012
Peripheral mononuclear cells	has-miR-107, miR-133a, miR-148a, miR-200c, miR-381, miR-425-3p, miR-494, miR-517b, miR-579, miR-589, miR-636, miR-652, miR-941, miR-1243	Belzeaux et al., 2012
Whole blood cells (12 weeks of treatment with escitalopram)	hsa-miR-130b, hsa-miR-505, hsa-miR-29b-2, hsa-miR-26b, hsa-miR-22, hsa-miR-26a, hsa-miR-664, hsa-miR-494, hsa-let-7d, hsa-let-7g, hsa-let-7e, hsa-miR-34c-5p, hsa-let-7f, hsa-miR-629, hsa-miR-106b, hsa-miR-103, hsa-miR-191, hsa-miR-128, hsa-miR-502-3p, hsa-miR-374b, hsa-miR-132, hsa-miR-30d hsa-miR-500, hsa-miR-770-5p, has-miR-589, hsa-miR-183, hsa-miR-574-3p, hsa-miR-140-3p, hsa-miR-335, hsa-miR-361-5p	Bocchio-Chiavetto et al., 2012
PBMC study in MDD patients	miRNA-26b, miRNA-1972, miRNA-4485, miRNA-4498, and miRNA-4743	Fan et al., 2014
Fluoxetine treatment	MiR-19 and target gene SERT	Launay et al., 2011
Acute and chronic ECS treatment	BDNF modulation associated increased miR-212	Ryan et al., 2013
Genetically modified mouse model	miR-135 associated with anxiety-and depression-like behaviors, 5HT levels, and behavioral response to antidepressant treatment	Issler et al., 2014
Genetic polymorphism and late insomnia in MDD	rs76481776 polymorphism in the pre-miR-182 associated with Clock genes	Saus et al., 2010
Genetic polymorphism and P300 latency in MDD	P300 latency in MDD patients was associated with miR-30e ss178077483 genotypes and the individuals with the C/T genotype had a longer P300 latency than those carrying the C/C genotype.	Xu et al., 2010