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MicroRNAs in Depression and Suicide: Recent Insights and Future Perspectives

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Abstract

Suicide is a major public health concern. A significant proportion of depressed individuals show suicidal ideation. The currently available medications are not optimal and a large number of depressed/suicidal patients do not respond to these medications. Thus, there is an urgent need to fully understand the neurobiological mechanisms associated with depression and suicidal behavior and to find novel targets for therapeutic interventions. In this regard, microRNAs (miRNAs), member of small non-coding RNA family, have emerged as an invaluable tool not only to understand disease pathogenesis but also to precisely pinpoint the targets that can be developed as drugs. In this review, these aspects have been discussed in a comprehensive and critical manner.

Keywords

miRNAs; depression; suicide; stress; neural plasticity; biomarker

Introduction

Suicide is a major public health concern. Approximately one million people commit suicide worldwide each year and 40,000 people commit suicide in the United States alone (CDC (Centers for Disease Control and Prevention), 2014; WHO (World Health Organization), 2012). The lifetime suicide attempt rate among adults is approximately 10%; among adolescents, suicide is the 3rd leading cause of death after motor vehicle accidents and homicide (CDC (Centers for Disease Control and Prevention), 2013). Major depression is frequently associated with suicidal behavior and a large proportion of depressed individuals show suicidal ideation (Farmer et al., 2001; Gramaglia et al., 2016; Kessler et al., 2005). Although much work has been done to characterize depression and suicidal behavior, a large number of depressed/suicidal patients do not respond sufficiently to the currently available medications (Fava and Davidson, 1996). This is partially attributed to the lack of full

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understanding of the neurobiological mechanisms associated with these disorders (Levinstein and Samuels, 2014).

Emerging evidence suggests that pathogenesis of mood disorders and suicide involves altered plasticity of neuronal pathways. In fact, it has been proposed that mood disorders/suicide result from an inability of the brain to make appropriate adaptive responses to environmental stimuli as a result of impaired synaptic and structural plasticity. Support for this idea comes from studies demonstrating consistent changes in the expression of genes that are critical in synaptic and structural plasticity (Dwivedi et al., 2006; Dwivedi et al., 2001; Dwivedi et al., 2009; Leistedt and Linkowski, 2013; Ota and Duman, 2013). In addition, changes in the synaptic circuitry (Aganova and Uranova, 1992), synaptic connectivity (Honer, 1999), and dendritic morphology (McEwen, 2000; Toni et al., 1999) have been reported during depression and suicidality. Although the underlying mechanisms of such compromised neural plasticity and structural impairments are not clearly understood, it is becoming increasingly evident that these disorders may result from disruptions across whole cellular signaling networks, leading to aberrant information processing in the circuits that regulate mood, cognition, and neurovegetative functions (Leistedt and Linkowski, 2013). In recent years, the emergence of small non-coding RNAs (RNAs that do not code for proteins) as a mega controller of gene expression has gained attention for their role in various disease processes. Among various non-coding RNAs, microRNAs (miRNAs) are the most studied and well characterized and have emerged as a major regulator of neural plasticity and higher brain functioning (Im and Kenny, 2012; Smalheiser et al., 2011). Therefore, their roles in neuropsychiatric diseases, such as schizophrenia, autism, Parkinson's disease, Huntington's disease, Tourette's syndrome, Fragile X syndrome, DiGeorge syndrome, and Alzheimer's disease have been studied extensively (Miller and Wahlestedt, 2010; Xu et al., 2012). The role of miRNAs in depression and suicidal behavior is still in its nascent stage; however, several lines of evidence, including pre-clinical and clinical, demonstrate that miRNAs may play a critical role in the development of stress-related disorders including depression and suicidal behavior (Gururajan et al., 2016; Lopez et al., 2014a; Lopez et al., 2014b; Ma et al., 2016; Roy et al., 2017b; Smalheiser et al., 2012). The present review article critically evaluates these aspects and discusses their relevance in diagnosis and therapeutic approaches.

Synthesis of miRNAs

miRNAs are encoded within primary miRNA (pri-miRNA) gene transcripts that could be inter-or intragenic. miRNA genes are transcribed to long primary miRNA by RNA polymerase II or III. The pri-miRNAs are then processed by RNase III enzyme Drosha to form small hairpin miRNA precursors (pre-miRNAs) that are generally 60 to 100 nt long and fold into a stem-loop structure. This process requires DiGeorge syndrome critical region 8 (DGCR8) protein as a cofactor. Together with DiGeorge, Drosha forms a large complex known as the "microprocessor complex." Drosha removes the flanking segments and ~11 bp stem region of the pri-miRNA. The pre-miRNAs are then transported out of the nucleus via the exportin. Pre-miRNAs are released to cytoplasm upon hydrolysis of GTP to GDP. The pre-miRNAs are further processed in the cytoplasm by RNase III enzyme Dicer, which converts pre-miRNAs into double-stranded mature small RNAs (miRNA/miRNA* duplexes)

of approximately 22 nt long (Chendrimada et al., 2007; Chendrimada et al., 2005; Gregory et al., 2005). Dicer requires cofactors such as TAR RNA-binding protein (TRBP) or PKR-activating protein (PACT). One of the miRNA/miRNA* duplexes is loaded onto an Argonaute homologue protein (Ago, isoforms of eIF2c) to generate the effector complex, known as RNA-induced silencing complex (RISC). The other miRNA* strand is degraded (Ha and Kim, 2014).

RISC recognizes short sequence within the 3' untranslated region (3'UTR) of target genes. This short region on target gene bears sequence complementarity (partial or full) to the "seed-sequence" of targeting miRNAs. The RISC-mediated imperfect binding of miRNA seed sequences with its target gene via Watson-Crick base-pairing often leads to translational inhibition of mRNAs. Because the RISC/miRNA complex recognizes target mRNA based on a seed region complementarity containing 2–7 nucleotides, it provides a mechanism by which one miRNA can target several mRNAs (Brodersen and Voinnet, 2009). RISC can also associate with 60s ribosome and eIF6 (Chendrimada et al., 2007) which can modify polysome formation and expose target mRNAs for degradation (Chendrimada et al., 2007). miRNA mediated destabilization of target mRNA transcript via deadenylation of poly A tail is another mechanism by which miRNAs suppress expression of specific mRNAs (Wu et al., 2006).

Besides regulating translational process, miRNA can also regulate gene transcription by targeting transcription factors, which in turn can lead to reduced expression of mRNAs and consequently reduced protein synthesis (Kosik, 2006; Michalak, 2006). miRNA biogenesis can also be regulated at the epigenetic level (Tardito et al., 2013). For example, inhibitors of DNA methylation and histone deacetylases can affect expression of several miRNAs (Chuang and Jones, 2007). On the other hand, a subset of miRNAs can control the expression of epigenetic regulators, such as DNA methyltransferases, histone deacetylases and polycomb group genes, leading to transcriptional activation of protein coding genes (Sato et al., 2011).

Role of miRNAs in regulating genes critical in stress response

Glucocorticoids regulate the hypothalamic-pituitary-adrenal (HPA) axis through a negative feedback mechanism while binding to soluble glucocorticoid receptors (GRs) in the pituitary and the hypothalamus and inhibit the release of corticotropin-releasing factor and adrenocorticotropic hormone. Expression of GRs is downregulated in depressed individuals (Pariante and Miller, 2001). GR protein is under constant regulation by miRNAs (Vreugdenhil et al., 2009), specifically, miR-124a and miR-18a bind to 3'UTR of GR gene and downregulate its expression (Vreugdenhil et al., 2009). Overexpression of miR-18a attenuates glucocorticoid-induced leucine zipper, a gene induced by stress-like levels of glucocorticoid. Interestingly, it has been found that miR-18a-mediated downregulation of GR translation is important in susceptibility to stress (Uchida et al., 2008). Turner and colleagues (Turner et al., 2010) recently predicted several possible miRNA binding sites within the GR first exon, suggesting possible regulation of GR by miRNAs.

In order to examine the miRNA response to stress, recently, we examined the effects of chronic corticosterone (CORT) treatment on miRNA expression in rat cortex (Dwivedi et al., 2015). Expression analysis revealed differential regulation of 26 miRNAs (19 upregulated, 7 downregulated) in CORT-treated rats. Interaction between altered miRNAs and target genes showed dense interconnected molecular network, in which multiple genes were predicted to be targeted by the same miRNA. A majority of altered miRNAs showed binding sites for GR element, suggesting that there may be a common regulatory mechanism of miRNA regulation by CORT. Functional clustering of predicted target genes yielded disorders, such as developmental, inflammatory, and psychological, that could be relevant to depression and suicidal behavior. Prediction analysis of the two most prominently affected miRNAs miR-124 and miR-218 resulted into target genes that have been shown to be associated with depression and stress-related disorders. Altogether, our study suggests miRNA-mediated novel epigenetic mechanism by which chronic CORT may be involved in depression and suicide pathophysiology.

Several types of stressors have also been utilized to examine their impact on miRNAs. Using unpredictable chronic mild stress combined with separation, it has been found that 13 specific miRNAs are altered in rat hippocampus (Cao et al., 2013). These include downregulated miR-298, -130b, -135a, -323, -503, -15b, -532, and -125a and upregulated miR-7a, miR-212, - 124, -139, and -182. Among these, miR-125a and -182 recovered to normal after intervention with antidepressant medication.

The effect of acute and chronic restrained stress on the expression of miRNAs in various brain areas have also been studied (Rinaldi et al., 2010). For example, it was found that acute stress induced a transient increase in the expression of miR-9, -9*, -26b, -29b, -30b, -30c, -30e, - 125a, -126-3p, -129-3p, -207, -212, -351, -423, -487b, -494, -690, -691, -709, -711, and let-7a in the frontal cortex but not in hippocampus. Some of these miRNAs (let-7a, -9, -26a/b, -30b/c, and-125a) showed increase in their expression 5 days after acute stress. Interestingly, their expression levels were not altered after repeated restraint stress. These results suggest that acute stress modulates miRNA expression rapidly to external stimuli, which could be due to altered synaptic efficacy through the regulation of localized mRNA translation.

Using chronic immobilization stress paradigms, it was found that the expression of several miRNAs was differentially altered in the central amygdala and the CA1 region of the hippocampus of rats during acute and chronic stress, with chronic stress causing much larger changes than acute stress (Meerson et al., 2010). Some of the miRNAs that were altered during acute and chronic stress include: miR-134, -183, -132, let-7a-1, miR-9-1, and -124a-1. Interestingly, except miR-let-7a-1, the expression of stress-responsive miRNAs were different in the two analyzed brain regions. In the CA1 region, miR-376b and miR-208 increased whereas miR-9-1 decreased under both acute and chronic stress conditions. Stress-responsive miR-134 and -183 target many splicing factors, such as SC35, SRP46, and SFRS11. SC35 promotes the alternative splicing of acetylcholinesterase from the synapse-associated isoform AChE-S to soluble AChE-R protein and the expression of SC35 is increased during stress. Thus, by regulating splicing factors and their targets, miR-183 and miR-134 may modify both alternative splicing and cholinergic neurotransmission in the

stressed brain. In addition, one of the targets of miR-183 is profilin 2, which regulates dendritic spine morphology in neurons. Interestingly, neurotransmitter homeostasis and behavior are severely affected in profilin 2 knockdown mice (Witke, 2004) and PFN2 expression is increased in lymphoblastoid cell lines of monozygotic twin pairs discordant for bipolar disorder (Matigian et al., 2007).

miR-134 is involved in the metaplastic downstream response to BDNF via suppression of Limk1, which affects dendritic spine morphology (Schratt et al., 2006). A range of miRNAs are involved in the regulation of synaptic scaling; (Fiore et al., 2009; Vo et al., 2005; Wayman et al., 2008) in particular, miR-132, -134, and -138 are implicated in dynamic dendritic synaptogenesis (Ye et al., 2016). Further, both miR-34a and -34c inhibit Notch signaling in the basolateral amygdala, which suppresses CRHR1-induced fear memory consolidation (Dias et al., 2014). Other research has shown that miRNAs regulate a wide range of stress-and fear-related neural mechanisms, including fear conditioning, extinction memory, and fear memory consolidation (Griggs et al., 2013; Lin et al., 2011). Therefore, miRNAs appear to be involved in dynamic cellular response to stressors. Recently, identification of miR-124-3p in epigenetically regulating glutamatergic receptor system has added another layer of intricacy to understand the molecular basis of depression (Roy et al., 2017a). This study focused on identifying the effect of miR-124- 3p on Gria4 expression in the frontal cortex of rats showing depressive phenotype. The report also showed the role of promoter DNA methylation in regulating miR-124-3p expression in prefrontal cortex of depressed subjects.

miRNAs in Early-Life Stress (ELS)

In recent years, there has been a great interest in identifying risk factors associated with early-life stress and development of depression and suicidal behavior. Interestingly, recent studies demonstrate that miRNAs may play a critical role in early-life stress. For example, expression levels of several miRNAs (miR-9, miR-29a, miR-124, and miR-132) are altered in the medial prefrontal cortex in 14-day-old rats following (MS) maternal separation (Uchida et al., 2010). At day 60, two miRNAs: miR-124 and -132 (along with miR-212), remained upregulated, suggesting stable changes in these miRNAs by ELS. As mentioned earlier, miR-124 targets GR (Vreugdenhil et al., 2009). Interestingly, GR activation suppresses miR-132 expression, which in turn decreases expression of BDNF, a gene linked to depression and suicidal behavior (Dwivedi, 2017). Methylation of a site (cg04927004) close to miR-124 has been linked to ELS in people with borderline personality disorder (Prados et al., 2015).

Interestingly, ELS alters several miRNAs at maturity in the brain. Recently, O'Connor and colleagues (O'Connor et al., 2013) compared early MS versus control animals at maturity (10–12 weeks) and conducted miRNA microarray analysis of hippocampus. Animals were also treated with fluoxetine, ECT, ketamine, or vehicle. MS altered expression of 24 miRNAs, while Fluoxetine, ECT, and ketamine altered 2, 10, and 14 miRNAs respectively. Of these, one miRNA, miR-598-5p, was common to all treatments. This supports the idea that early trauma produces changes in a modest number of miRNAs, which can be modulated by antidepressants.

miRNAs in Coping Response to Stress

Differences in miRNA expression can also influence an individual's coping response to a stressor. This has been demonstrated in an animal model where Fischer 344 rats were found to be more refractory to stress-induced HPA axis habituation than Sprague-Dawley rats. The habituation process involved the gradual dampening of HPA axis response towards repeated stress. Being a stress hypersensitive strain, Fischer 344 rats showed heightened HPA axis response to acute stressors with a parallel increase in CORT secretion. This HPA axis hyperactivity and concomitant increase in CORT level was the result of reduced GR expression. Reduced protein level of GR in paraventricular nucleus (PVN) of F344 rats was post-transcriptionally regulated by miR-18 expression, causing an overall decrease in negative HPA axis feedback inhibition (Uchida et al., 2008).

Chronic stress-induced increased glucocorticoid level has been shown to cause dendritic atrophy in hippocampal neurons (Magarinos et al., 2011; Magarinos and McEwen, 1995). Reduced BDNF expression appeared to be the underlying cause of this neural atrophy. Interestingly, data from in-vitro cortical neuron culture show diminished expression of BDNF via glucocorticoid, which can lead to miR-132 associated expression downregulation. Pharmacological intervention by MAPK/ERK1/2 inhibitors (U0126 and PD98059) in the upstream pathway of BDNF causes similar miR-132 downregulation. This indicates BDNF associated role of miR-132 as neuronal trophic factor sensitive to glucocorticoid-induced neuronal stress (Kawashima et al., 2010).

The role of miRNAs in the development of depressive behavior has recently been studied by the Dwivedi group (Smalheiser et al., 2011). In this study, it was found that specific miRNAs were distinctly associated with LH behavior (vulnerable to develop depression) compared to non-learned helpless (NLH) rats (resistant to develop depression). NLH rats showed adaptive response to the expression of miRNAs. As part of this adaptive response, a large set of miRNAs (miR-96, 141, 182, 183, 183*, 298, 200a, 200a*, 200b, 200b*, 200c, and 429) were significantly downregulated in NLH group compared to those who were not given stress but tested for learned helpless behavior. These miRNAs were encoded at a few shared polycistronic loci, suggesting that this downregulation was coordinately controlled at the level of transcription. Interestingly, most of these miRNAs were enriched in the synaptic fraction. They also share common 5' seed sequence motifs, which make them a specialized cluster of miRNAs with the potential to regulate a set of overlapping targets to achieve a common functional role. This finding was further supported when half of the miRNAs from the downregulated set was identified to target CREB1 gene by participating in a feedback loop (Wu and Xie, 2006), which involved eight miRNAs (miR-96, -182, -183, -200a, -200b, -200c, -220a*, and -200b*) containing putative CREB1 binding site on their upstream sequence. In addition, a core miRNA co-expression module, consisting of 36 miRNAs that were highly correlated with each other across individuals of the LH group (but not in the NLH or TC groups), was identified. The presence of such module implied that the normal homeostatic miRNA response was not merely absent or blunted in LH rats; rather, gene expression networks were actively reorganized, supporting their acquired phenotypic changes in behavior.

Increased coping-like behavior in stress response has also been demonstrated in socially defeated stressed rats with marked changes in miR-135 expression after administering imipramine acutely or chronically (Issler et al., 2014). Overexpression of miR-135, specifically in 5HT neurons, represented reduced anxiety and depression-like behavior after stress induction. Selective inhibition of 5HT1A receptor and Slc6a4 transcripts from serotonergic system was mediated via miR-135 in a genetically engineered mouse model (Issler et al., 2014). Overexpression of miR-135 had antidepressant property with a detrimental effect on 5HT level. On the other hand, miR-135 knock down mouse model showed inability to respond to antidepressant treatment as well as increased anxiety-like behavior (Issler et al., 2014). These findings collectively demonstrate that miR-135 associated expression increase was able to repress an array of 5HT system-related transcripts, including SERT and presynaptic HTR1A levels, causing an increase in 5HT in the synaptic cleft, and possibly resulting in reduced depression phenotype.

Under chronic stress, compromised hippocampal neurogenesis was related to miR-17-92 cluster expression. Overexpression of miR-17-92 was able to reverse stress-induced defects in hippocampal neurogenesis (Jin et al., 2016). A reciprocal relationship between predicted target gene Sgk1 and miR-17-92 was validated as contributing factor behind the altered hippocampal neurogenesis under stress-induced depression (Jin et al., 2016). Similar stress related resiliency was related to miR-15a expression in amygdala of socially defeated mice. However, miR-15a overexpression in basolateral amygdala (BLA) was not sufficient to cause behavioral deficits associated with exposure to chronic social defeat stress. Instead, behavioral changes in stress-induced mice were primarily associated with reduced level of miR-15a expression and a reciprocal increase in FKBP51 expression. FKBP51 was identified as a direct target of miR-15a. Altogether, this study showed that miR-15a plays an anxiolytic role and helps in developing an adaptive response towards chronic stress (Volk et al., 2016).

Human Postmortem Brain Studies Showing Dysregulated miRNAs in Depression and Suicide

Transcriptome-wide miRNA expression changes have been found to be associated with depression and suicide. A study from the Dwivedi group showed an overall miRNA expression downregulation in prefrontal cortex, which was noted as molecular signature of depressed suicide subjects (Smalheiser et al., 2012). Identification of 21 significantly downregulated miRNAs as a cluster in depressed group and their close chromosomal localization suggested their coordinated regulation. When analyzed individually, almost half of the downregulated miRNAs were found to be encoded at chromosomal loci near another miRNA and were possibly transcribed by the same pri-miRNA gene transcripts (miR-142-5p and 142-3p; miR-494, 376a*, 496, and 369-3p; miR-23b, 27b and 24-1*; miR-34b* and 34c; miR-17* and 20a). In addition, 3 pairs of miRNAs were encoded at distances greater than 100 kb but still found to lie within the same chromosomal region (miR-424 and 20b at Xq26.2-3, 377 kb apart; miR-142 and 301a at 17q22, 820 kb apart; miR-324-5p and 497 at 17p13.1, 205 kb apart). This suggested that at least some of the downregulated miRNA expression was due to decreased transcription. Sharing identical seed sequences between

altered miRNAs (miR-20a and 20b; miR-301a and 130a; and miR-424 and 497) identified from their 5'-end sequence comparison was an indication of a cohesive nature of gene regulatory function attributed towards their common gene targets. In the cellular context, the ability of a single miRNA to regulate multiple target genes and single gene targeted by multiple miRNAs opens up the opportunity to build up an extensive gene regulatory network; most often, this bears disease specific signature influenced by pathological changes. This might have been the case shown by the Dwivedi group (Smalheiser et al., 2012), demonstrating an overall blunted response in miRNA expression associated with depression related cellular changes, thus allowing an epigenetic repatterning in cortical neurons. Besides demonstrating a pronounced influence on coordinated gene regulatory network, this study also showed a unique pattern of miRNA co-expression network, constructed by a set of 29 miRNAs, extensively interconnected in the depressed group. Pair-wise correlation between miRNAs showing a co-regulated expression was used to map this miRNA network in order to identify coherently regulated miRNAs responding to a common environmental cue. Several of the 29 miRNAs (let-7b, miR-132, 181b, 338-3p, 486-5p, and 650) were found to be hubs, extending their connection to 4-9 other miRNAs in the network; however, this pair-wise correlation based miRNA network was completely missing in the control group. This shows an identification of a synergistic miRNA network bearing an exclusive mark associated with depression pathophysiology. Further analysis of predicted target genes identified a list of candidates known for their significant role in cellular growth, differentiation, signaling and plasticity (UBE2D1, UBE2W, CAMK2G, AKAP1, SMAD5, MITF, BACH2, MYCN, GABRA4, and CACNA1C). Careful analysis of target genes including both predicted and validated (DNMT3B, BCL2, VEGFA, NOVA1) demonstrated a range of molecular functions such as splicing, cellular apoptosis, DNA methylation, axonal growth (Smalheiser et al., 2012). Many of them were implicated in functions related to depression neurobiology as identified from previous studies using both clinical population and preclinical animal models.

Trkb-T1, a BDNF receptor lacking a tyrosine kinase domain, was reported to be downregulated in the prefrontal cortex of the suicide brain (Ernst et al., 2009; Ernst et al., 2011). This was found to be linked with elevated level of miR-185* (Maussion et al., 2012). TrkB-T1 is highly expressed in astrocytes and regulates BDNF-evoked transient calcium influx (Rose et al., 2003). Bioinformatic analysis and in-vitro cell culture experiments validated the presence of three functional binding sites of miR-185* on 3' UTR of Trkb-T1 gene. The increase in miR-185* expression was further confirmed in a larger cohort of suicide completers which demonstrated a significant negative correlation with Trkb-T1 expression in the prefrontal cortex (Maussion et al., 2012).

In a different study, metabotropic glutamate receptor GRM4, a receptor protein of glutamatergic, dopaminergic, GABAergic and serotonergic neurotransmission, was found to be affected by brain-enriched miR-1202 in the prefrontal cortex of depressed subjects (Lopez et al., 2014b). A significant downregulation was noted for miR-1202 in depressed brain; this downregulation was negatively correlated with GRM4 expression. This finding implicates the neurobiological role of GRM4 and miR-1202 in regulating depression-like behavior (Lopez et al., 2014b). In another study, epigenetic modification of glial cell line-derived neurotrophic factor (GDNF)-mediated signaling cascade in glial population of the

depressed brain mediated by miR-511 has been reported (Maheu et al., 2015). Several studies show the involvement of GDNF in the pathogenesis of depression as well as in antidepressant response. Thus, identifying GDNF as target of miR-511 and finding a marked increase in miR-511 expression in depressed subjects partially explains the role of this miRNA in depression related behavioral changes and considerable neuroplastic adaptations.

Besides affecting genes related to either neurotransmission or neurotrophic factors, a recent report shows the involvement of miRNAs in modulating neuropeptide functions in the suicide brain (Aschrafi et al., 2016). This study found a negative influence on urocortin 1 (Ucn1) gene expression mediated by miR-326 in the rostroventral midbrain area within the centrally projecting Edinger–Westphal nucleus (EWcp) of suicide subjects. In the same brain area, the expression of Ucn1 was also decreased due to overexpression of miR-365 in chronic variable mild stress model of depression in rats.

In the prefrontal cortex of MDD suicide subjects, miR-218 influences the expression variability of DCC (netrin-1 guidance cue receptor gene, deleted in colorectal cancer) gene. Reduced expression of DCC in PFC neurons was related to increased resiliency against stress-induced depression. As DCC receptors have the ability to control axon arborization, dendritic growth, and synapse formation, the loss of an antagonizing effect of miR-218 on DCC may possibly lead to repatterning of synaptic connections in the pyramidal neurons in the MDD brain (Torres-Berrio et al., 2017).

Proinflammatory cytokines have recently received considerable attention for their role in suicidal behavior; however, how the expression of cytokine genes is regulated is not clearly known. The Dwivedi group recently examined the underlying mechanisms of critical cytokine gene tumor necrosis factor-alpha (TNF-α) dysregulation in the brains of individuals who died by suicide (Wang et al., 2018). An elevated level of TNF-α was noticed in the dorsolateral prefrontal cortex (dlPFC) of individuals who died by suicide regardless of psychiatric diagnosis. Similar type of increased TNF-α expression was identified in individuals with major depressive disorder who died by causes other than suicide (Wang et al., 2018). This change in TNF-α expression was paralleled with an increased miR-19a-3p expression in dlPFC of suicide completers. Similar upregulation of TNF-α and miR-19a-3p was observed in the peripheral blood mononuclear cells of depressed patients with suicidal ideation. This study was able to establish a direct interaction between miR-19a-3p and TNF-α 3’UTR using an in-vitro cell culture system. Although the canonical role of miRNA in regulating target gene expression comes through a repressive effect at post-transcriptional level, this study identified a complex epigenetic regulation on TNF-α via RNA-binding protein HuR in suicide brain which demonstrated a 3’UTR specific molecular sequestration from the repressive effect of miR-19a-3p (Wang et al., 2018).

Alterations in metabolic enzymes of the polyamine system have been reported to play a role in predisposition to suicidal behavior (Fiori et al., 2011). Recently, Lopez and colleagues (Lopez et al., 2014a) examined whether the dysregulation of polyamine genes in depressed suicide completers could be influenced by miRNAs. These investigators 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 completers and controls using qRT-PCR

were profiled, it was found that several miRNAs showed significant upregulation in the prefrontal cortex of suicide completers compared to psychiatrically-healthy controls (miR-124, -139-5p, - 195, -198, -320c, -33b, 34a, -34c-5p, -497, -873). However, they found that only miR-139-5p and miR-320c were inversely correlated with polyamine gene SAT1, whereas miR34c-5p and miR-320c were inversely correlated with polyamine gene SMOX. These results suggest a relationship between miRNAs and polyamine gene expression in the suicide brain and postulate a mechanism for SAT1 and SMOX downregulation at the post-transcriptional level.

Very recently, the Dwivedi group studied the expression of miRNAs in locus coeruleus (LC) of suicide subjects, a brain area implicated in suicidal behavior (Roy et al., 2017b). It was found that not only was the expression of miRNAs substantially altered in the LC of suicide subjects, but miRNAs as well as target genes formed specific networks that can be crucial in underlying etiopathogenesis of suicide. A total of 754 miRNAs were analyzed; of these, 367 miRNAs were further examined after normalization. The expression of a core group of 13 miRNAs was significantly altered in the LC of suicide subjects compared with healthy control subjects. Of them 10 were upregulated (miR-17-5p, -20b-5p, -106a-5p, -330-3p, -541-3p, -582-5p, -890, -99b-3p, -550-5p, -1179) and 3 were downregulated (miR-409-5p, let-7g-3p, miR-1197). Construction of an integrated gene regulatory network based on predicted target genes of altered miRNAs showed a comprehensive association with neuropsychiatric disorders, which included major depression and anxiety, the two important risk factors associated with suicidal behavior. In addition, mapping of cellular pathways, affected by these altered miRNAs, indicated an overall change in cellular signaling that have been implicated in suicide neurobiology. Moreover, the formation of a miRNA network, which appeared to be specific to suicide but not the control group, was noted.

Studying chromosomal localization of miRNA clusters helps understand coordinated regulation of miRNA expression under specific pathophysiological conditions. In the same study mentioned above (Roy et al., 2017b), it was observed that miRNAs, whose chromosomal localizations were in proximity (e.g., miR-20b-5p, -106a-5p and -890 on chromosome X, miR- 330-3p and -99b-3p on chromosome 19, and miR-409-5p and -1197 on chromosome 14), had the same direction of changes and similar fold changes. This happened even in those miRNAs whose transcriptional units were in opposite directions (miR-330-3p and -99b-3p on chromosome 19). This notion signifies the evolutionary conservation pattern of gene regulation which may culminate into similar functional output. This also has relevance from the perspective of disease pathophysiology in which LC may be regulating functional gene networks in a cohesive manner by orchestrating the coordinated transcriptional output of the altered miRNAs.

Peripheral miRNAs in depressed and suicidal individuals

miRNA can be detected in circulating biological fluids such as serum, plasma, urine, saliva and CSF (Cogswell et al., 2008; Hanke et al., 2010; Weber et al., 2010). Emerging evidence show that circulating form of miRNA has the potential to reflect the changes associated with CNS related disorders (Rao et al., 2013; Sheinerman and Umansky, 2013). More interestingly, disease associated changes in miRNA profile of peripheral blood were found to

be highly correlative with the changes in neuronal tissue of various CNS related neurodevelopmental and degenerative disorders (Gaughwin et al., 2011; Liu et al., 2010). Under healthy conditions, these miRNAs are stably expressed in blood cells; however, under pathological conditions, the profile of miRNAs changes significantly, suggesting that peripheral miRNAs can possibly be used as a reliable biomarker under disease conditions. Furthermore, the changes elicited in miRNA expression profile of blood samples due to therapeutic administration of drugs can predict the systemic response to a specific treatment regime (Gamez-Pozo et al., 2012; Murakami et al., 2010). Even though the blood based free circulating miRNAs have been shown to be extremely useful for detecting and following the course of human cancer, myocardial infarction, and neurodegenerative conditions, including Alzheimer's disease, Parkinson disease, Huntington disease, and prion disease (Chen et al., 2008; Dorval et al., 2013; Fichtlscherer et al., 2010; Jin et al., 2013; Ma et al., 2013), they suffer from major limitations due to their heterogeneous sources and their restricted expression within different compartments of blood. Recent discovery that living cells, including neurons can actively secrete miRNAs in response to known activating signals, examining brain specific miRNA can be used as a promising source of biomarker for CNS disease (Kalani et al., 2014). The actively secreted miRNAs are enclosed in exosomes, which can cross blood-brain barrier (Alvarez-Erviti et al., 2011; Lakhal and Wood, 2011; Valadi et al., 2007; Vickers et al., 2011) and are well protected from degradation (Keller et al., 2011). 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 proteincoding genes (Cortez et al., 2011). Evidence showing that exosomal miRNAs are excreted physiologically in response to stress lends credence that they can be used as potential biomarker candidate (Mendell and Olson, 2012).

Belzeaux and colleagues were the first to show transcriptome-wide changes in miRNA expression using a small patient cohort assessed for their major depressive episodes (Belzeaux et al., 2012). Profiling of miRNA expression in peripheral blood mononuclear cells (PBMCs) was done in 16 severely depressed patients and 13 matched controls at baseline, and 2 and 8 weeks after antidepressant treatment. miRNAs that showed changes between depressed and controls at baseline were: has-miR-107, -133a, -148a, -200c, -381, -425-3p, -494, -517b, -579, -589, -636, -652, -941, and -1243. Only 2 miRNAs showed stable overexpression in depressed patients during the 8-week follow-up compared with controls (miR-941 and -589). They also identified miRNAs exhibiting significant variations of expression among patients with clinical improvement (7 upregulated and 1 downregulated). Fourteen dysregulated miRNAs had putative mRNA targets that were differentially expressed in depressed subjects, suggesting a common RNA regulatory network function in depression. This study was also able to correlate changes in miRNA expression as observed by the Dwivedi group in postmortem cortex of MDD subjects (Smalheiser et al., 2012).

Overall change in miRNA expression in response to antidepressant treatment was documented under a whole-miRNome quantitative study involving 10 MDD subjects (Bocchio-Chiavetto et al., 2013). The blood-based expression profiling demonstrated changes in 30 miRNAs after 12 weeks of treatment with escitalopram. A large-scale change was observed in upregulated class of miRNAs which showed increased expression of 28

miRNAs, whereas two miRNAs were found to be downregulated. Functional assessment short listed 13 miRNAs (let-7d, let-7e, miR-26a, -26b, -34c-5p, -103, -128, -132, -183, -192, -335, -494 and -22) with pervasive role in the neural plasticity and stress response. miR-132 has been implicated in regulating neurogenesis and synaptic plasticity, primarily stimulating axonal and dendritic outgrowth in different brain areas (Mellios et al., 2011). This miRNA, together with miR-26a, miR-26b and miR-183 widely contribute to the neurotrophic action of BDNF (Caputo et al., 2011; Kawashima et al., 2010; Wayman et al., 2008). Furthermore, 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 roles in the pathogenesis of psychiatric disorders and in the mechanism of action of antipsychotic drugs and mood stabilizers. Moreover, postmortem studies in the brains of bipolar disorder patients show increased levels of miR-22* in the prefrontal cortex (Kim et al., 2010). On the other hand, miR-494 and miR-335 are downregulated in the prefrontal cortex of depressed suicide patients (Smalheiser et al., 2012). The target genes of these altered miRNAs include: BDNF, GR, NR3C1 and the nitric oxide synthase NOS1, growth factors (IGF1, FGF1, FGFR1, VEGFa and GDNF), calcium channels (CACN41C, CACNB4, SLC6A12 and SLC8A3) and neurotransmitter receptors (GABRA4 and 5-HT4); some of these have been implicated depression and in the mechanism of action of antidepressants.

More recently, an association between miRNA processing gene variants and depression has been found (He et al., 2012). The investigators genotyped three polymorphisms from three miRNA processing genes (DGCR8, AGO1, and GEMIN4) in a case-control study including 314 patients and 252 matched healthy controls. Frequencies of genotypes and alleles showed significant difference between depressed patients 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 improved response to antidepressant treatment, whereas the variant of AGO1 rs636832 showed decreased risk of suicidal tendency, suicidal behavior, and recurrence. Whereas allele frequency showed a significant difference when compared to 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 depression and GEMIN4 rs7813 did not affect susceptibility to depression. These observations suggested that miRNA processing polymorphisms may affect depression/suicidal risk and treatment.

The role of miR-182 has recently been identified in depression (Li et al., 2013). Cellbased modeling showed miR-182 as a regulator of BDNF gene, which was similar to miR-132. Using neuronal cell model, it was demonstrated that the expression of BDNF was downregulated by both miR-182 and miR-132. Comparison of healthy controls, and patients with depression showed lower serum BDNF level and higher miR-132 and -182 levels in depressed patients. 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 was observed. In addition, a reverse relationship between the serum BDNF levels and the miR-132/miR-182 levels in depression was found. Collectively, this study suggests that miR-182 is a putative BDNF-regulatory miRNA and may be utilized as biomarker in the diagnosis and treatment of depression. Strength of

miRNA-based biomarker prediction using peripheral blood mononuclear cells (PBMC) in a set of 81 depressed patients was recently validated by identifying marked expression related changes in 26 miRNAs (Fan et al., 2014). Further validation confirmed the upregulation of 5 miRNAs (miRNA-26b, -1972, -4485, -4498, and -4743) with predicted downstream target genes known for their role in pathways related to CNS functions. In a recent study, an interesting observation was noticed in miRNA expression in depressed patients while analyzing their cerebrospinal fluid (CSF) as well as serum specimens (Wan et al., 2015). A significant change in 4 miRNAs was observed in both serum and CSF from the same patients: 3 of the miRNAs were upregulated (miR-221-3p, -34a-5p, and let-7d-3p) and one was downregulated (miR-451a). This study was able to establish the face value of representative miRNAs as biomarker of MDD in serum with similar casual changes in CSF.

The possible use of brain enriched miRNAs in predicting clinical depression has recently been shown in serum samples of 18 MDD patients (Roy et al., 2017a). Serum based screening demonstrated 3.5-fold increase in miR-124-3p expression after adjusting the result for age, gender and race in MDD cohort. This finding was similar to the one reported in the post-mortem brain of MDD subjects (Roy et al., 2017a). Moreover, this study was further supported by an observation of a striking decline in miR-124 expression monitored in 32 MDD patients after eight weeks of antidepressant treatment (He et al., 2016). Similar upregulated expression of miR-19a-3p was found when examined in PBMC of 12 depressed subjects with severe suicidal ideation. Although this study was limited by a small population size, miR-19a-3p expression was not confounded with gender, age, or race/ethnicity effects. Therefore, specific change in miR-19a-3p expression might be influenced by strong suicidal thoughts in depressed patients. However, these miRNA associated expression changes cannot be confirmed in suicidal ideation because of a lack of examination of depressed patients without suicidal ideation (Wang et al., 2018).

The variability in antidepressant response, especially in treatment-resistant depressed cases, is poorly understood. Thus, identifying potential markers which can correlate with treatment response will be of critical importance. In a recent report, involvement of four miRNAs (miR-146a-5p, -146b-5p, -425-3p and -24-3p) in predicting the treatment responsiveness of the antidepressant, duloxetine, was shown. Significantly altered expression of these 4 miRNAs, after antidepressant treatment and identification of downstream signaling pathways with known functions in depression pathophysiology (e.g., MAPkinase/Wnt), suggest their role as predictive biomarkers for treatment response in depressed patients (Lopez et al., 2017).

Conclusion and Future Directions

In this review, we presented evidence of the involvement of miRNAs in depression and suicidal behavior. Studies demonstrating the role of miRNAs in depression and suicide are listed in Table 1. These studies indicate that miRNAs, particularly those that are involved in synaptic plasticity, neurotrophic activity, and stress response may be critically associated with the development of depressive behavior. Some studies, including our own, suggest that it is possible to distinguish miRNAs that are associated with resiliency or development of depressive behavior. These miRNAs show adaptive response to stress and thus cause

resistance to depression. This was confirmed in both animal and human postmortem brain studies. In fact, the overexpression of neuron-specific miRNA miR-124 in specific brain area of mice has been shown to cause depressive behavior or resistance to antidepressant response (Bahi et al., 2014). Individual miRNAs have also been studied for their role in regulating specific genes that are critical in depression or stress-related disorders. They can individually be targeted to modify specific cellular signaling in order to restore their aberrant functions noted in depression; however, one has to be cautious that depression is a heterogeneous disorder and suicidal behavior has several endophenotypes. Thus, establishing a very specific set of miRNAs for these diseases may not be appropriate. Interestingly, so far, a majority of the studies have examined miRNAs and associated gene networks. This may be a right approach; however, as has been discussed earlier, miRNAs also coordinate their expression in a cohesive manner. In our animal and human postmortem brain studies (Roy et al., 2017b; Smalheiser et al., 2012; Smalheiser et al., 2011), we have detected specific sets of miRNAs that were highly interconnected and were associated with vulnerability to depression or suicidal behavior when compared to groups which were resilient or healthy. The resilient and healthy subjects showed another specific set of coordinated miRNAs. Thus, establishing the coordinated network of miRNAs will be crucial in identifying individuals who will be at risk for developing depression/suicidal behavior.

Another aspect that needs attention is the examination of cell type-specific regulation of miRNAs. miRNAs are expressed in brain-region as well as cell type specific manner. Also important is to examine the potential reasons for altered miRNA expression. Is it because of genetic changes in the promoter region upstream of primary miRNA gene transcripts, the pre-miRNA hairpin, or the mature miRNA or due to RNA editing of transcripts or epigenetic suppression of the chromosomal region encoding the miRNAs? A variety of enzymes are responsible for processing miRNAs. These include Drosha, Dicer and cofactors DGCR8, TRBP, and PACT. Several of these proteins have been shown to be modified post-translationally in a dynamic manner. For example, altering the relative expression of eIF2c may change the efficiency of translational arrest produced by a given miRNA (Azuma-Mukai et al., 2008). Recently, it has been shown that dicer is activated by proteolytic cleavage under conditions of elevated calcium levels (Lugli et al., 2005; Smalheiser et al., 2008), and eIF2C undergoes reversible phosphorylation within cells, which is required for its translocation to processing bodies (Zeng et al., 2008). The phosphorylation of eIF2C appears to be due to the activation of ERK1/2 (Zeng et al., 2008). Since abnormalities in calcium-sensing proteins and ERK1/2 signaling in the brain of depressed suicide subjects has been found (Dwivedi, 2011; Dwivedi et al., 2006; Dwivedi et al., 2001; Dwivedi et al., 2009), it will be worthwhile asking whether dicer cleavage patterns or eIF2C phosphorylation are altered in these subjects. One can also examine whether there is any genetic link between miRNA and depression and suicide. Such genetic linkage has been reported in specific miRNAs in schizophrenia (Mellios and Sur, 2012).

The presence of miRNAs in peripheral tissues, particularly in blood cells, provide a promising approach to use them as potential biomarker for both diagnosis and treatment response. Table 2 depicts recent studies showing miRNAs as biomarkers for depression/suicidal behavior. However, there are several caveats that need to be considered for the use of blood based circulating miRNAs as biomarker. For example, the source of miRNAs in

blood cells is not clear at the present time and there is a possibility that changes in circulating miRNAs may not be directly related to changes in the brain. The other caveat is that peripheral miRNA studies have not been replicated so far. Whether it is related to different clinical phenotypes associated with major depression is not clear and needs further evaluation. In addition, no other major psychiatric disorder has identified a specific transcriptome-based, reliable, clinically useful peripheral blood test to aid in diagnosis. This shows the limitation of blood based biomarkers in diagnosing specific psychiatric illnesses. Despite these limitations, it appears that miRNA based biomarkers may be promising, given that some of the miRNAs are leaked into circulating blood, which can be assessed easily.

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Highlights

- miRNAs play critical roles in gene regulation at post-transcriptional level.
- miRNAs are involved in stress response, an important factor in suicidal behavior.
- miRNAs have emerged as an invaluable tool to understand disease pathogenesis.
- miRNAs may be clinically useful in diagnosis and treatment response.

Table 1:

miRNAs as Epigenetic Modifier in MDD-Suicide Brain

Study #	Brain areas	Participating miRNAs	Target Genes	References
1	Dorsolateral prefrontal cortex	miR-142-5p, miR-33a, miR-137, miR-489, miR-148b, miR-101, miR-324-5p, miR-301a, miR-146a, miR-335, miR-494, miR-20b, miR-376a*, miR-190, miR-155, miR-660, miR-552, miR-453, miR-130a, miR-27a, miR-497, miR-10a, miR-20a, miR-142-3p	UBE2D1 and UBE2W, CAMK2G, AKAP1, SMAD5, MITF, BACH2, MYCN, GABRA4, and CACNA1C	Smalheiser et al., 2012
2	Frontal cortex	miR-185	TrkB.T1	Maussion et al., 2012
3	Prefrontal cortex	miR-139-5p, miR-320c, miR-34c-5p	SSAT1, SMOX	Lopez et al., 2014a
4	Prefrontal cortex	miR-1202	GRM4	Lopez et al., 2014b
5	Basolateral amygdala	miR-511	GFR1	Maheu et al., 2015
7	Edinger-Westphal nucleus (EWcp) of rostroventral midbrain area	miR-326	UCN1	Aschrafi et al., 2016
8	Prefrontal cortex	miR-218	Netrin-1 guidance cue receptor gene, deleted in colorectal cancer (DCC)	Torres-Berrio et al., 2017
9	Ventral prefrontal cortex	miR-146a-5p, miR-146b-5p, miR-425-3p, miR-24-3p	MAPK/WNT signaling pathway	Lopez et al., 2017
10	Locus coeruleus	miR-17-5p, miR-20b-5p, miR-106a-5p, miR-330-3p, miR-409-5p, miR-541-3p, miR-582-5p, miR-890, let-7g-3p, miR-99b-3p, miR-550-5p, miR-1179	RELN, GSK-3β, MAOA, CHRM1, PLCB1 and GRIK1	Roy et al., 2017a
11	Prefrontal cortex	miR-19a-3p	TNF-α	Wang et al., 2018

Table 2:

Use of miRNA as potential molecular marker in major depressive disorder (MDD) and suicidal patients

Study #	Source	Participating miRNAs	Clinical Diagnosis	References
1	**Peripheral blood mononucleocyte**	**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**	**MDD**	Belzeaux et al., 2012
2	**Blood serum**	**miR-132 and miR-182**	**MDD**	Li et al., 2013
3	**Peripheral blood mononucleocyte**	**miRNA-26b, miRNA-1972, miRNA-4485, miRNA-4498, and miRNA-4743**	**MDD**	Fan et al., 2014
4	**Cerebrospinal fluid**	**miR-221-3p, miR-34a-5p, let-7d-3p, miR-451a**	**MDD**	Wan et al., 2015
5	**Blood serum**	**miR-124-3p**	**MDD**	Roy et al., 2017b
6	**Peripheral blood mononucleocyte**	**miR-124-3p**	**MDD**	He et al., 2016
7	**Whole blood**	**miR-146a-5p, miR-146b-5p, miR-425-3p, miR-24-3p**	**MDD**	Lopez et al., 2017
8	**Peripheral blood mononucleocyte**	**miR-19a-3p**	**MDD-Suicide**	Wang et al., 2018