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Annals of Psychiatry and Mental Health

Review Article

microRNAs as Biomarker in Depression Pathogenesis

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Abstract

Major depressive disorder (MDD) is a major health concern with alarming rates of completed suicide. Thus, it is important to understand the pathophysiology of this disorder. In addition, disturbingly high rates of relapse and low rates of recovery make it urgent not only to develop targeted treatments but to identify biomarkers that can predict treatment response for individual patients. MicroRNAs (miRNAs) are a class of small non-coding RNAs that control gene expression by modulating translation, mRNA degradation or stability of mRNA targets. The role of miRNAs in disease pathophysiology is emerging rapidly. Several recent studies have suggested the possible role of miRNAs in synaptic plasticity, neurogenesis, and stress response, all implicated in MDD. Emerging studies showthe direct role of miRNAs in the development of depression phenotype. More recently, the role of miRNAs in prognosis and treatment response is being considered for various disease pathophysiology, including MDD. The review discusses the recent studies demonstrating the role of miRNAs in MDD and whether miRNA can be used as a biomarker for MDD pathogenesis and treatment response.

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Submitted: 21 October 2013

Accepted: 26 November 2013

Published: 02 December 2013

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Keywords

- Major depression
- microRNA
- Biomarker
- Plasma
- Stress

INTRODUCTION

Major depressive disorder (MDD) affects about 20% of the population at some point in their lives [1,2]. Interestingly, about 40% of MDD patients do not respond to the currently available medications [3,4].This is partially a result of poor understanding of the molecular pathophysiology underlying MDD. It is becoming increasingly evident that MDD may result from disruptions across whole cellular networks, leading to aberrant information processing in the circuits that regulate mood, cognition, and neurovegetative functions. Recently, microRNAs (miRNAs), a prominent class of small non-coding RNAs, has emerged as a major regulator of neural plasticity and higher brain functioning [5,6]. By modulating translation and/or stability of a large number of mRNA targets in a coordinated and cohesive fashion, they are able to regulate entire genetic circuitries.[7] These miRNAs are expressed highly in neurons, and because they can regulate the expression of hundreds of target mRNAs, neuronal miRNA pathways can create an extremely powerful mechanism to dynamically adjust the protein content of neuronal compartments even without the need for new gene transcription [8,9].

miRNAs are small (~22 nt) non-coding RNA transcripts, which by binding to the 3' UTR of specific mRNA targets, regulate their translation and/or stability. The miRNAs are encoded within primary miRNA gene transcripts (pri-miRs) that may be intergenic (away from known protein-coding genes) or may be located within introns of protein-coding host genes [10,11]. The pri-miRs are transcribed by pol II, may be spliced, and may acquire a poly-A+ tail. The pri-miRs are then processed further within the nucleus by Drosha and other co-factors to form one or a series of small hairpin miRNA precursors, or pre-miRs that are generally 70-110 nt. long and fold into a stem-loop structure. The pre-miRs are then transported out of the nucleus, and the stem regions are further processed by Dicer and other co-factors to form a double-stranded small RNA about 22 nt. long. Generally, one of these strands is preferentially incorporated into a complex with one or more Argonaute homolog proteins (isoforms of eIF2c). Thus, one has a single-stranded mature miRNA of ~22 nt. in length, which, 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-UTR region of mRNAs, and can interfere with translation of the mRNA and/or may reduce mRNA levels. Besides the direct sequence-specific interaction of RISC with mRNAs, other proteins that bind nearby sites within the 3'-UTR (e.g., FMRP homologues, HuB family members and other ARE binding proteins) may control the magnitude and even the direction of miRNA effects. Indeed, in certain situations, depending on the phase of the cell cycle in dividing cells, miRNAs may actually enhance rather than inhibit translation [12]. Finally, miRNAs can also inhibit or stimulate transcription of certain genes [13]. MicroRNAs tend to act in co-regulated groups, and to affect groups of targets as part of larger gene expression networks that contain feedback and feedforward regulatory loops [14].

miRNAs have been strongly implicated in many neuronal functioning: a) Conditional knockout of dicer in postnatal post-mitotic neurons results in gradual neurodegeneration or cell shrinkage and altered function [15-17]; b) In Drosophila, one of the RISC proteins, armitage, is necessary for LTP and synaptic protein synthesis, and is cleaved during the learning process [18]. In mammalian forebrain, local control of protein synthesis near synapses is thought to be critical for normal learning and dendrite spine morphogenesis [19]; c) Loss of the FMRP causes Fragile X syndrome in humans and produces a related spectrum of behavioral, learning, dendritic spine and LTP deficits in fmr1 knockout mice. FMRP regulates protein synthesis by binding to specific sites within the 3'-UTR of certain mRNAs, and probably does so in concert with miRNAs and the RISC complex [20]; d) LIM kinase 1, a protein that regulates dendritic spine growth, is itself repressed locally within dendrites by miR-134, and BDNF de-represses the effects of this miRNA [21]. This relationship is noteworthy since LIMK1 is strongly down-regulated in a rat model of learned helplessness [22] and BDNF expression is altered in depression [23]; e) CREB1, a key protein regulating long-term changes in gene expression, is important for learning and LTP and is down-regulated in depression [24]. CREB1 (and FMRP and HuB) are among a set of major hubs for miRNA regulation, insofar as their 3'-UTR regions contain "short seed" recognition sites for over 40 miRNAs. Conversely, many miRNA genes have binding sites in their promoter regions for CREB1 among many other transcription factors [25] and at least several (e.g., miR-132) have been shown to be activity-dependent and induced by BDNF acting via CREB. Overexpression of miR-132 enhances neurite outgrowth and dendritic morphogenesis in cultured cortical neurons [26]. CREB and BDNF, participate in a variety of feedback and feedforward networks involving miRNAs [27] so that it may be more correct to say that miRNAs are involved in regulating homeostasis of biochemical pathways, rather than simply inhibiting expression of individual targets. In addition, there is a tendency for miRNAs to target mRNAs that are under complex regulation (e.g., having both long 5'-UTRs and long 3'-UTRs), and that are alternatively spliced. Preferential targets include proteins that function at post-ligand stages of signaling pathways, e.g. receptors, adaptor proteins, and transcription factors. Thus, there is a strong rationale for expecting that miRNAs will play an important role in regulating pathways that are affected in depression.

Several studies have suggested the role of miRNA in neurogenesis, an important aspect in depression and in the mechanisms of action of antidepressants (for detailed reviews please see reference [6]). To examine whether miRNAs can participate in the pathogenesis of MDD, we examined miRNA expression in frontal cortex of rats who developed behavior (learned helpless [LH]) that resembles stress-induced depression and in those who did not develop depression (non-learned helpless [NLH]), even though they received similar inescapable shocks [28]. In this manner, we were able to distinguish the factors associated with the development of depression phenotype.We found that NLH rats showed a robust adaptive miRNA response to inescapable shocks whereas LH rats showed a markedly blunted miRNA response. One set of miRNAs showed large, significant, and consistent alterations in NLH rats, consisting of 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. All were down regulated in NLH rats relative to tested controls (no-shock group), and all showed a blunted response in LH rats. Because these miRNAs are down regulated in NLH rats, but not LH rats, this can be interpreted as a homeostatic response. In addition, we identified a large core co-expression module, consisting of miRNAs that are strongly correlated with each other across individuals of the LH group, but not either 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.

Interestingly, stress responsive gene glucocorticoid receptor (GR), which is down regulated in depressed individuals [29] is under constant regulation of miRNAs.miR-124a and miR-18a bind to 3'UTR of GR gene and downregulate its expression [30]. Overexpression of miR-18a attenuates glucocorticoid-induced leucine zipper, a gene induced by stress-like levels of glucocorticoid. It is possible that higher expression of miR-18a and consequent downregulation of GR could be responsible for the genetic susceptibility to stress as has been shown in genetic stress rat model [31].Several types of stressors have also been utilized to examine how miRNAsrespond to stressors [32,33]. Interestingly, acute and chronic restrained stress cause differential changes in the expression of miRNAs in a brain region-specific manner such that acute stress modulates miRNA expression quickly to external stimuli by changing their synaptic efficacy through regulation of localized mRNA translation [32].

The effect of early-life stress, one of the critical factors in the development of depressive disorders [34], can also lead to altered expression of miRNAs [35]. For example, maternal separation can enhance stress vulnerability to repeated restraint stress exposure in adulthood. At the molecular level, maternal separation increases the expression of Repressor element-1 silencing transcription factor (REST) 4. Transient overexpression of REST4 in the medial prefrontal cortex of neonatal mice produces depression-like behaviors in adults after repeated exposure to restraint stress, suggesting that REST4 may play a role in the development of stress vulnerability. REST regulates the expression of several miRNAsthat are involved in brain development and plasticity [36,37].

In a recently study, we examined the role of miRNAs in depression by examining global expression of miRNAs in the prefrontal cortex of depressed subjects [38]. We found that 24 microRNAs were significantly decreased in the depressed group. In addition, 29 other miRNAs showed a trend for alterations in the suicide group (miR-515-3p, 211, 511, 424, 517a, 500*, 215, 369-3p, 597, 302b, 496, 517c, 184, 34a, 520c-3p, 34b*, 24-1*, 594, 34c-5p, 372, 17*, 545, and 565). The down-regulated miRNAs include many miRNAs that have been implicated in cellular growth and differentiation. The set comprises both very abundant and low-abundance miRNAs, and those with high and low synaptic enrichment as studied in mouse homologues [39]; the miRNAs arise from both intronic and intergenic loci, and are located on numerous chromosomes. However, many of the

miRNAs in this set show relationships with one other. Almost half of the miRNAs are encoded at chromosomal loci near another miRNA on the list and are presumably transcribed by the same primary miRNA gene transcripts [28,29]: a) mir-142-5p and 142-3p; b) mir-660 and 500*; c) mir-494, 376a*, 453, 496, and 369-3p; d) mir-515-3p, 517a, 517c, 520c-3p, and 372; e) mir-23b, 27b and 24-1*; f) mir-34b* and 34c; and g) mir-17* and 20a. In addition, three pairs of miRNAs are encoded at distances greater than 100 kb but still lie 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 down-regulated miRNAs also share 5'-seed sequences (particularly bases 2-8) that are involved in target recognition. For example, identical seed sequences are shared by a) mir-20a and 20b and mir-301a and 130a. As well, a 6-mer nucleotide motif is shared by mir-34a, 34b* and 34c, and strikingly, a 5-mer motif (AGUGC) within the 5'-seed is shared by 9 of the affected miRNAs (mir-148b, 301a, 130a, 20a, 20b). This suggests that the down-regulated miRNAs should exhibit overlap among their mRNA targets. Target analysis revealed that many of these are transcription factors (e.g., E2F1, BACH1, SP1, HOXA5, RUNX1) and other nuclear proteins, and also include transmembrane as well as signaling proteins. Intriguingly, 2 different down-regulated miRNAs target VEGFA (mir-20b, 20a), a molecule implicated in depression. Other validated targets include DNMT3B (mir-148b) and MYCN (mir-101, 34a).

Further evidence of the role of miRNA in depression comes from studies showing polymorphisms in pre-miR-30e [40] and pre-miR-182 [41]. Reduced affinity of miR-95 due to the presence of a SNP (rs13212041) in the 3′UTR of the 5-HT1B mRNA leads to aggressive behavior in humans [42]. miRNA sequences are also present in the 3'-UTR region of TPH1 and TPH 2 genes, presumably modulating the production of 5-HT [43]. In addition, 5-HT_{2A} receptors undergo constitutive repression by miR-195 and are phasically repressed by the activation of miR-15 [43]. Both TPH and $5HT_{2A}$ have been implicated in depression [44-46].

Because overwhelming evidence points the role of miRNAs in depression pathogenesis, it is critical to examine if these miRNAs can be detected in peripheral tissues and can be used as a biomarker. Interestingly, miRNAcan be detected in circulating biological fluids such as serum, plasma, urine, saliva and CSF [47-49].Surprisingly, 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 be used as a reliable biomarker under disease conditions. Recently, blood cell 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, prion disease [50-54].

Circulating miRNAs arise from heterogeneous sources and are expressed within different compartments of blood. For neuropsychiatric perspective, it is imperative to characterize miRNAs in blood cells that are brain-derived. In this respect, it has been shown that miRNAs can be released actively or passively from neurons into the circulating blood [50,51]. These miRNAsare enclosed in exosomes or microvesicles and are protected by RNA binding proteins. Recently, it has been shown that in schizophrenia patients, several circulating miRNAs have been identified as potential disease biomarker [55]. Plasma miR-134 levels in drug-free, 2-week medicated, and 4-week medicated bipolar mania patients were significantly decreased when compared with controls, and its level increased following medication [56]. Decreased circulating miR-134 level both in drug-free and medicated patients showed negative correlation with the clinical scales, suggesting that decrease in plasma miR-134 levels may be directly associated with the pathophysiology and severity of manic symptoms in BD [56].

The use of miRNAs as peripheral biomarker in MDD is gaining momentum. Belzeaux et al. [57] followedmiRNA expression profile in peripheral blood mononuclear cells (PBMCs) of severe MDD patients and controls at baseline, and 2 and 8 weeks after treatment. Changes in several miRNAs were noted at base line. Also, twomiRNAs showed stable overexpression in MDD patients during the 8-week follow-up compared with controls (miR-941 and miR-589).

In a whole-miRNome quantitative analysis in the blood of MDD subjects after 12 weeks of treatment with escitalopram, Bocchio-Chiavetto et al. [58] found that 30 miRNAs were differentially expressed after the escitalopramtreatment. 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 which have been implicated the MDD and in the mechanism of action of antidepressants.

CONCLUSION

From the above mentioned clinical studies, it is clear that miRNAs are significantly altered in MDD. On the other hand, animal model system studies show that alterations in miRNAs can lead to depressive phenotype. The presence of miRNAs in peripheral tissues, particularly, in blood cells provide promising approach to use miRNAs as potential biomarker for both diagnosis and treatment response. There are several issues that need consideration for the use of circulating miRNAs as biomarker. For example, the source of miRNAs in blood cells is not clear at the present time. In this regard, exosomal miRNAs can be useful in detecting miRNAs of neuronal origin. There is a possibility that changes in circulating miRNAs may not be directly related to the changes in the brain. While this complicates the study of circulating miRNAs, miRNAs still appear to have promise to be useful biomarkers, since it is likely that they reflect systemic alterations that accompany the disease process (e.g. chronic stress, inflammatory and neuroimmune processes).

ACKNOWLEDGEMENT

The research was supported by grants from National Institute of Mental Health (R01MH082802; R21MH081099; R21MH091509; 1R01MH101890), American Foundation for Suicide Prevention, and University of Illinois at Chicago Clinical and Translational Sciences National supported by Center for Advancing Translational Sciences, National Institutes of Health (Grant # UL1TR000050).

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Cite this article

Dwivedi Y (2013) microRNAs as Biomarker in Depression Pathogenesis. Ann Psychiatry Ment Health 1(1): 1003.