Chapter 1

Role of miRNA in Major Depressive Disorder

Saurabh Srivastav, Mahino Fatima, Amal Chandra Mondal*

Cellular and Molecular Neurobiology Lab, School of Life Sciences, Jawaharlal Nehru University, India

***Corresponding Author:** Amal Chandra Mondal, Cellular and Molecular Neurobiology Lab, School of Life Sciences, Jawaharlal Nehru University, New Delhi-110067, India, Email: acmondal@mail.jnu.ac.in

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Abstract

Depression is a common neuropsychiatric disorder affecting 350 million people worldwide and is considered to be one of the major contributors to the overall burden of disease. In this context, Major Depressive Disorder (MDD) is one of the most common forms of depression associated disorder that involve increased risk of suicide and is associated with psychosocial deterioration with poor quality of life and disability. MDD severely affects the social life of an individual with profound effect on individual relationships and in extreme condition it leads to suicide. The underlying aetiology of disease is not yet clear, but several risk factors have been identified which mainly include environmental risk factors, negative cognition, temperament, gender, and genetic components. Studies on MDD subject has revealed a close association with compromised neural circuitry both at the structural and functional level. Brain functions involving regulation of mood and other cognitive function requires optimized and normalized brain circuitry network. Aberration in such circuit will directly affect cognitive function, thereby leading to neuropsychiatric illness. In this milieu, synaptic plasticity optimization both in structural and functional level is critical for neuronal network integrity. The regulation of such function requires multiple components and a class of small non-coding RNAs; miRNAs have gained a lot of attention as their levels are shown to be dysregulated

in MDD subject both in post-mortem and peripheral tissue sample. In the present chapter, the role of miRNAs in MDD has been highlighted and their potential use as a biomarker in clinical diagnosis of disease has been discussed.

Introduction

Depression is a common neuropsychiatric disorder and as per World Health Organization (WHO) report, it is estimated that worldwide 350 million people of all ages suffer from depression. It is the leading cause of disability and being the major contributor to the overall global burden of the disease (http://www.who.int/mediacentre/factsheets/fs369/en/). In this milieu, MDD is one of the most widespread neuropsychiatric disorders involving increased risk of suicide and is colligated with psychosocial deterioration, poor quality of life and disability [1], morbidity, and mortality [2,3]. Based on DSM-5 (Diagnostic and Statistical Manual-5) criteria, MDD is a condition manifested by feeling of guilt; lack of interest in activities; and sleep disturbances [4]. In the majority of MDD cases, significant weight change is also observed [4]. MDD is diagnosed across the lifespan with a female population being affected three fold more than their male counterpart. Moreover, younger population (under 19 years) are also being diagnosed with MDD and extreme condition of MDD leads to suicide [4]. The underlying aetiology of disease is not yet clear, but several risk factors have been

identified which mainly include environmental risk factors, negative cognition, temperament, gender, and genetic components [4,5]. The Genetic component is an important risk factor as heritability of MDD is around 40%, and individuals with familial history of depression are at 2-4 fold greater risk contrary to the general population with no familial history [4].

Further, MDD severely affects the social life of an individual with profound effect on individual relationships, as it is depicted from the fact that withdrawal from activities is one of the diagnostic features. Therefore, an individual suffering from MDD is likely to withdraw from friends and family members, thereby affecting relationship leading to social isolation, guilt and worthlessness. In extreme conditions, this leads to suicide attempts and death/ that ends life [6]. Although there are several symptomatic treatments available, but most of the people are either less or not aware of the proper medication. Moreover, approximately 40% of the patients do not respond to medication which is currently available for treating MDD [7]. This unresponsiveness towards medication is a challenge and underlying cause points toward our understanding of the underlying molecular mechanism associated with aetio-pathophysiology of MDD.

Studies on MDD subject has revealed a close association with/ between compromised neural and structural plasticity [8], which is depicted from the findings that

individuals with MDD have alteration in synaptic connectivity and circuitry in different brain regions including prefrontal cortex [9], and frontal lobe [10]. Moreover, altered dendritic morphology in hippocampal neuron [11] along with the reduction in neuron and glial cell number in cortical area is also observed [12]. It is also observed that learning and memory processes are negatively affected in the milieu of MDD [13].

Although aforementioned evidences provide information regarding alteration in brain regions, both at structural and functional levels, but the underlying molecular mechanism which leads to such condition is not yet clearly understood. Hence, further studies in this context are required to decipher the aetiopathology of MDD. However, it is clear that alteration in such complex process has a multifactorial basis and that it is not regulated by any single process. Further, it is worth mentioning that complex brain functions involving regulation of mood and other cognitive function require optimize and normalized brain circuitry network. Aberration in such circuit will directly affect cognitive function, thereby leading to neuropsychiatric illness. In this milieu, synaptic plasticity optimization both at structural and functional level is critical for neuronal network integrity. Modulation of such neuronal plasticity is achieved both by a protein coding sequence of associated genes and regulatory element of gene [14]. Moreover, the advances in understanding of

associated gene and network have provided initial clues toward aetiology of neuropsychiatric disorder like MDD, Schizophrenia (SZ) and Bipolar disorder (BPD) [15]. In this context, a class of non-coding RNAs known as microRNAs (miRNAs) have been shown to play important role in the regulation of complex cellular function [16,17]. These miRNAs species are potentially known to regulate hundreds of their target transcripts by modulating both transcript stability and translation thereby regulating entire gene network and associated pathways [15]. Further, recent evidences have highlighted miRNAs as a potential player in the aetio-pathophysiology of mental aberration. It is corroborated from the findings that several miRNAs are found to be dysregulated as per studies from post-mortem brain samples of subject with neuropsychiatric disorders [15]. In this milieu, miRNAs role in MDD has been highlighted in recent years [15,18] and other neuropsychiatric disorders, including SZ [15,18,19], and BPD [15,17,18] thereby indicating the importance of miRNAs in neuropsychiatric illness. In addition, miRNAs dysregulation in circulatory peripheral sample in neurological disorder have provided a mean of utilizing it as a potential biomarker for disease diagnosis [18]. This particular is important as disease diagnosis is difficult in complex neuropsychiatric disorders due to existing comorbidities among different psychiatric disorders. Therefore, miRNAs and their role in MDD are discussed in the present chapter to provide a better understanding of miRNA in MDD.

miRNAs

miRNAs are small non-coding RNA species (~22 nucleotides) and are evolutionary conserved. They are known to play key role in regulation of gene expression at the post-transcriptional level. In this process, miRNA binds to its specific target mRNA 3' UTR region, which triggers either suppression or degradation of target mRNA [20,21], However, they are also known to activate translation of mRNA in some cases [22]. The biogenesis of miRNA involves transcription of miRNA genes in order to form primary transcript (pri-miRNA) having extended hairpin structure [21]. It is followed by processing of pri-miRNA within the nucleus by Drosha and DGCR8 (DiGeorge syndrome critical region 8) to form precursor miRNA (pre-miRNA) of approximately 70 nucleotides which have a stem loop structure [23,24]. After the formation of pre-miRNA, it is transported from nucleus to cytoplasm by Exportin5. This is followed by cleavage of 70 nucleotide pre-miRNA into ~22 nucleotides double stranded mature miRNA by Dicer. Lastly, one of the strands of newly form mature miRNA is loaded into RNA induced silencing complex (RISC) which comprises of Dicer, transactivating response RNA-binding *protein* (TRBP) and Argonaute 2 [25]. RISC loaded with its specific miRNA, targets its specific mRNA by binding it with miRNA seed region and thereby modulating gene expression [21]. The process described above is illustrated in figure 1.

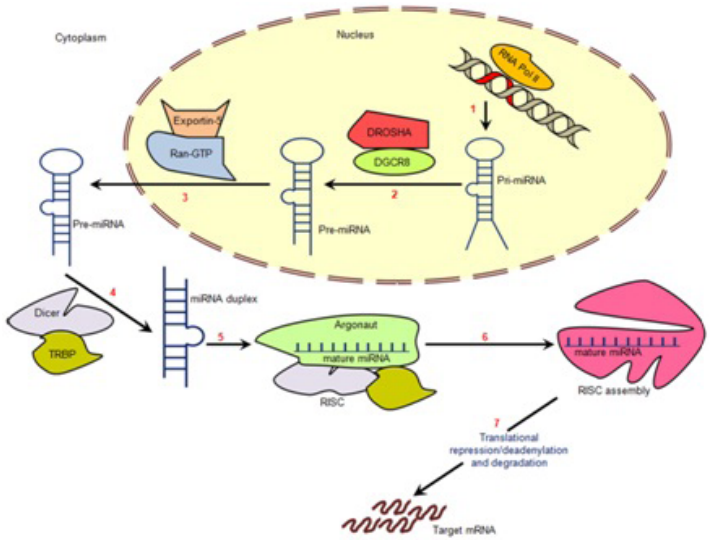

Figure 1: miRNA biogenesis and function. 1, RNA polymerase II (RNA Pol II) transcribe miRNA gene to form primary miRNA (Pri-miRNA); 2, precursor miRNA (pre-miRNA) from Pri-miRNA is formed through its processing by DROSHA and DGCR8 (DiGeorge syndrome critical region *protein* 8); 3, pre-miRNA is transported into cytoplasm mediated by Exportin-5 and Ran-GTP; 4, miRNA duplex formation by cleavage of pre-miRNA through Dicer (double-stranded RNA endoribonuclease III); 5, one of the strand of miRNA duplex as mature miRNA bind to Argonaut followed by RISC (RNA induced silencing complex) assembly; 6, Functional RISC complex having mature miRNA with Argonaut, Dicer and TRBP (transactivating response RNA-binding protein) is formed. The RISC complex, so formed targets its miRNA specific mRNAs for either their repression or degradation.

miRNA in MDD

Since the discovery of miRNAs, these small non-coding RNA species have been continuously gaining a lot of attention as they have been shown to involve in regulation of gene expression and are found to be associated with various disease aetiopathologies including neurodevelopmental and neuropsychiatric disorders [15-18]. Recent year, research has shown the involvement of miRNAs in MDD, although only few studies are available in this context, but they have provided initial insight [26-31]. Based on these studies [26-30], it seems, that miRNA is one of the key players in MDD disease outcome, and participates in disease pathogenesis, as miRNA levels are dysregulated in MDD subject. This dysregulation is found in other neuropsychiatric disorders like SZ, BPD and Autism Spectrum Disorder (ASD) [15,17,32,33]. Further, miRNAs studies on MDD subject have revealed that Pre Frontal Cortex (PFC) from post-mortem brain sample [35,36,37] and peripheral tissue sample [26-31] exhibit miRNA dysregulation. Thus, it clearly implicates that miRNA alterations are not only present in specific brain region, but also occurs in peripheral blood and serum samples of MDD subject. This is important as circulating miRNAs are gaining a lot of attention in a way to utilize them as a molecular signature in disease diagnosis [18]. Studies have reported that there are several miRNAs which are either upregulated or downregulated in MDD subject and thus implicate their

crucial role in MDD [26-31,35-37]. The details of miRNAs studies on MDD subject are summarised in table 1.

Table 1: miRNAs in major Depressive Disorder.

Sample	miRNAs	Status in MDD	Method	References
Postmortem tissue (PFC)	miR-142-5p, miR-137, miR-489, miR-148b, miR-101, miR-324-5p, miR-301a, miR-146a, miR-335, miR-494, miR-20a/b, miR-376a, miR-190, miR-155, miR-660, miR-130a, miR-27a, miR-497, miR-10a, miR-142-3p	Downregulated	qRT-PCR	[35]
Postmortem tissue (PFC)	miR-508-3p, miR-152-3p	Downregulated	TLDA array	[40]
Postmortem tissue (PFC)	miR-139-5p, miR-320c and miR-34c-5p	Upregulated	qRT-PCR	[41]
Postmortem tissue (PFC)	miR-1202	Downregulated	qRT-PCR	[37]
Blood	let-7d, let-7e, let-7f, let-7g, miR-22*, miR-26a, miR-26b, miR-29b-2*, miR-30d, miR-103, miR-106b*, miR-128, miR-130b*, miR-132, miR-140-3p, miR-183, miR-191, miR-335, miR-361-5p, miR-374b, miR-494, miR-500, miR-502-3p, miR-505*, miR-574-3p, miR-589, miR-629, miR-664	Upregulated	qRT-PCR	[31]
	miR-770-5p, miR-34c-5p	Downregulated		
Blood (PBMCs)	miR-517b, miR-636, miR-1243, miR-381, miR-200c	Downregulated	Microarray	[26]
	miR-589, miR-579, miR-941, miR-133a, miR-494, miR-107, miR-148a, miR-652, miR-425-3p	Upregulated		
Blood (serum)	miR-182, miR-132	Upregulated	qRT-PCR	[28]
Blood (PBMCs)	miR-26b miR-1972, miR-4485, miR-4498, and miR-4743	Upregulated	Microarray and qRT-PCR	[39]
Blood	miR-335, miR-583, miR-650, miR-708 and miR-654	Downregulated	qRT-PCR	[29]
	miR-644, miR-450b, miR-328, miR-182	Upregulated		
CSF and Blood	miR-221-3p, miR-34a-5p and let-7d-3p	Upregulated	qRT-PCR	[30]
	miR-451a	Downregulated		
Blood (Plasma)	miR-451a, miR-223-3p and miR-17-5p	Upregulated	qRT-PCR	[42]
	miR-320a	Downregulated		
Blood (PBMCs)	miR-124	Upregulatd	qRT-PCR	[43]

PFC: Prefrontal cortex; PBMCs: peripheral blood mononuclear cells; CSF: Cerebro spinal fluid; qRT-PCR: quantitative real time polymerase chain reaction

Further, it is important to mention that miRNAs are unique in a way that a single miRNA can target many mRNAs and simultaneously a single mRNA can be a target of different miRNAs, which means that the miRNAs are capable of regulating pathways that involves complex gene association and networks. This unique mode of action of miRNAs, make them a candidate of choice for studying complex neurological disorders that deal with neuropsychiatric component in it [38]. This is further supported by the finding that brain contains approximately 70% of the known miRNA [34].

In this milieu, the identified altered miRNAs in MDD subject are known to target components (such as serotonin transporter and metabotropic glutamate receptor 4) known to play crucial and significant roles in different pathways important to proper functioning of the brain and nervous system [29,37,39]. The target pathways include PI3K–Akt signalling, axon guidance, Wnt signalling, neurotrophin signalling, Hippo signalling, mTOR signalling, long-term depression [30]. Although, further studies are needed to decipher the role of miRNAs in regulating aforementioned identified pathways associated with MDD and its aetiology. This is important as identification of the combination of commonly associated dysregulated miRNAs in MDD will help in defining the underlying mechanism and associated pathways.

Further, the diagnosis of MDD is done based on DSM-V criteria [4], but still it is not perfect and requires

a high degree of precision, as there are several factors that lead to false diagnosis. One of which being the comorbidities, that most neuropsychiatric disorders share with each other. Therefore, the knowledge of molecular biomarker becomes very important in the precise diagnosis of MDD. Although, no such defined biomarkers information is available for MDD diagnosis. In this milieu, miRNAs are gaining attention as their altered level in diseased subject [26-31,35-37,40] has provided hope to utilize them as molecular signature. Although, post mortem sample from MDD subject have shown miRNA alteration [35-37], but they cannot be considered as source of sample for disease diagnosis in live patients. Therefore, peripheral samples like blood, serum can be utilized to look for miRNAs alteration, as studies [26-31,39,42,43] support miRNA dysregulation in peripheral samples of MDD subject.

The first report on peripheral miRNA profiling in MDD subject was carried by Bocchio-Chiavetto et al. [31], in which they evaluated the alteration in global miRNA levels in whole blood sample post to 12-weeks effective treatment with the antidepressant drug escitalopram. 30 miRNAs were observed to be modulated. Further, based on target gene prediction and pathway analysis, it was observed that these miRNAs have probable potential role in various signalling pathways important to brain function such as axon guidance, long term potentiation (LTP) and depression [31]. Since then, more studies have been carried out by different groups to look for peripheral miR-

NAs alteration in MDD and the prediction of the probable role based on pathway analysis [26-31]. Recently, one of the research groups have demonstrated that miRNA miR-124-3p potentially contributes in the pathophysiology of MDD, and it may also serve as a novel target for drug designing and as a biomarker for MDD [44]. However, more studies are required to identify and validate the combination of miRNAs which are dysregulated in peripheral samples of MDD subject. Thus, miRNAs offers immense potential to be utilized as molecular signature in disease diagnosis.

Further, utilization of circulating/peripheral miRNA as novel biomarker for disease diagnosis offers many advantages. It is worth mentioning that obtaining and analysing biomarker from any given clinical sample should be less tedious and precise. In this milieu, protein based biomarkers are attractive candidates of choice, but looking into complex neuropsychiatric disorders such candidates have many limitations. The most common being the post-translational modifications, the sequence variation among different tissues, etc which make the clinical diagnosis a tedious task. On the other hand, miRNAs not only exist in the extracellular environment of blood unlike other nucleic acid, but are also stable in different condition including the RNase rich blood environment [45]. Moreover, the miRNAs exhibit sequence specificity not only among different species but also detected in various tissues. Further, the detection of miRNAs can be easily carried out by qRT-

PCR and microarray based methods [18]. Also, miRNAs expression pattern varies based on pathophysiology and changes observed in circulation may reflect the changes in diseased tissue. Lastly, the miRNAs extraction from serum is simple and involves non-invasive process [18]. However, there are some limitation with miRNAs based clinical diagnosis, one of which being the selection of the reference control for comparison between the diseased and healthy subject.

Therefore, it is clear that miRNAs have an important role in neuropsychiatric disorders like MDD and they can be utilized as potential molecular signature in the disease prognosis evaluation during follow-up.

Conclusion

Therefore, it is clearly visible that miRNAs are important in the aetiology of MDD, as is reflected from various studies which confirm alteration/dysregulation of miRNAs in MDD subject both in post-mortem and peripheral tissue sample. More importantly, these altered miRNAs are involved in modulation of target genes that are crucial in several pathways critical for different brain functions. Although, studies have shown an association of miRNAs with MDD, but more studies are needed to further identify novel miRNAs and to validate known miRNAs which are dysregulated in MDD. Identification of a specific set of miRNAs, exclusive to MDD will enable researchers to look for their probable target using online Bioinformatics databse tools (e.g., www.targetscan.org; www.mirbase.

org). This would provide further information in decrypting the affected molecular pathways which are possibly involved in the aetiology of MDD. Therefore, such information will be beneficial in designing drug against such disorder based on molecular pathways affected. Further, neuropsychiatric disorders like MDD are difficult to diagnose, as they involve a complex range of symptoms, which includes depression, psychosis, mania, and deficits in cognitive function. Thus, clinical diagnosis of disease is difficult and identification of potential biomarker is essentially required in a way to ease diagnosis of MDD. In this context, miRNAs have emerged as a potential candidate, which is depicted from the finding that miRNAs are altered in peripheral samples of MDD subject. However, information regarding any such specific miRNAs based biomarkers is lacking, but recently one of the groups has shown that miR-124-3p may serve as a putative epigenetic signature of MDD. Therefore, further studies will definitely help in identification of specific set of miRNAs that may potentially serve as a molecular signature in disease diagnosis and will also enable researchers to design therapeutic strategies for ailments.

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