



# Use of MicroRNA as the Therapeutic Targets for Treatment of Major Depressive Disorder



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## Abstract

Major depressive disorder is a global disease burden. It is major psychiatric disorder in which the patients suffer from the serious dysfunctions of the cognitive system and deprivation of mood, anhedonia etc. Stress is the major contributory factor of the of depression and a large number of depression patients become the victims of suicide. Depression is associated with a number of degenberative changes in the brain associated with cognitive functions and mood. Current therapies of depression aim to restore the cognitive functions of the patient by promoting neurogenesis in their brain. However, all these types of therapies have many limitations which provoke us to develop a more efficient therapy for the treatment of major depression. In recent time, the uses of microRNAs in the treatment of many diseases have got popularities. In this present review we have discussed the possible advantages of using miRNA as the therapeutic target of major depression.

**Keywords:** Major depressive disorder; MicroRNA; Exosomes; Brain-derived neurotrophic factor

## Introduction

Major Depressive Disorder (MDD) is a major mental disorder in which patients consistently exhibit cognitive disturbances such as impairments in attention, learning and memory, executive functions etc. [1]. Other important symptoms of the disease include depressed mood, and anhedonia, loss of energy, feelings of worthlessness etc. that deteriorate the quality of life of the patient substantially [2]. At least 350 million people in the world at present are the victims of depression making it as a leading cause of disability globally [3]. Depression is associated with high suicidal incidences [4] and World Health Organization (WHO) predicted that by 2020 depression will become the second leading cause of global burden of disease [5]. Many studies have demonstrated that both in depression patients and in suicidal brains structural deterioration occur in brain regions implicated in higher cognitive functions [6-8]. People who do not suffer from depression exhibit a balance in degradation and regeneration processes of neurons in their brain. Depressed patients, on the other hand, show greater degradation of neurons that cause the reduction of their brain structures [9]. Thus it appears that, therapeutic induction of neurogenesis in patients by an effective method will make a new avenue towards the proper treatment of major depression. Currently available therapies such as treatment by antidepressants, deep brain stimulatton (DBS), electroconvulsive therapy (ECT) etc. induce neurogenesis in depression patients but all of these forms of treatments have many limitations. Antidepressant therapy for

MDD aims to enhance the neuroplasticity in patients and to prevent their brain atrophy thereby [10,11]. They promote neurogenesis by increasing the expressions of brain-derived neurotrophic factor (BDNF) [10,12] that enhances neuron differentiation and long term survival of the newborn neurons. Some examples of such antidepressant are selective serotonin re-uptake inhibitors (SSRIs), monoamine oxidase inhibitor (MAOI), selective norepinephrine reuptake inhibitors (SNRIs) etc. [10,13]. However, these antidepressants exhibit a number of limitations such as delayed onset of action, low response and remission rates, poor tolerability, persistent adverse effects etc. [14]. Electroconvulsive therapy (ECT) is not effective to all MDD patients [15] and shows risk of relapse of depressive episodes [16]. Deep brain stimulatton (DBS) is a useful therapeutic approach for MDD but it develops many problems associated with the neurosurgical procedures [17]. Owing to these many limitations of the currently available treatments of MDD, there is the need for an alternative and more effective therapy for this serious psychiatric disorder. As microRNA (miRNA) expressions in brain are altered both in human and in experimental animals with depressions, it seems possible that manipulations of miRNA expressions in brain may be useful for the treatment of depression [18]. In recent times, miRNAs (miRNAs) have been extensively studied as a promising therapeutic drug class with highly encouraging results in many diseases [19,20]. In this review we shall discuss about the prospect of miRNAs as potential

therapeutic targets for the treatment of MDD. Before that a brief discussion regarding the role of miRNAs in the etiopathology of depression will enable us to understand the origin of the concept of the therapeutic use of this tiny RNA molecule in the treatment of MDD.

### Biogenesis of miRNA

miRNAs belong to the most abundant class of small RNAs comprising 21-23 nucleotides whose main function is to down regulate the gene expression post transcriptionally. It has been estimated that miRNAs can regulate the expression of approximately 30% of the protein-coding genes in human. Since a single miRNA can regulate the expression of more than 100 different mRNAs, it is not surprising that their dysregulations may contribute to a variety of diseases [21,22]. miRNAs are initially generated as a transcript called primary miRNA (pri-miRNA) of 100-1000 nucleotides that is processed in the nucleus by an RNaseIII enzyme called Drosha to form small hairpins of 60-100 nucleotides known as precursor miRNA (pre-miRNA) and transported to cytoplasm. In the cytoplasm pre-miRNAs are further processed by another RNaseIII called Dicer to form a miRNA duplex of approximately 22 nucleotide length. One strand of the duplex by a combination with Argonaute (Ago) homologue protein forms a RNA-induced silencing complex (RISC) and the other strand is degraded. RISC binds to specific sequences located mainly within the 3'/untranslated region (3'/UTR) of the target mRNA and blocks their translation [22]. Thus it appears that miRNA are negative regulator of gene expression.

### Evidences, that Correlate the Role of miRNA in the Pathogenesis of MDD

Brains of animals with depressive behavior [23] and post-mortem brains of depressed human subjects [24] exhibited altered miRNA expressions indicating miRNA dysregulation might be responsible for the pathogenesis of depression. In one study [23], rats that showed chronic corticosterone induced depressive features exhibited profound dysregulation of miRNA in prefrontal cortex (PFC). Out of many miRNAs analyzed, 75% were upregulated and rests were down regulated in comparison to control animals. These altered miRNA expressions were probably the outcome of the responsiveness of the brain of the animals to hyperactive HPA axis as the serum corticosterone levels were also found to be elevated in these animals. In a recent study [25], chronic unpredictable mild stress (CUMS) induced depressed mice, compared to controls, exhibited the upregulation of many known miRNAs as well as some novel miRNAs in the medial prefrontal cortex (mPFC). A total of 40 mRNAs were significantly down regulated in this brain region most of which were predicted to be the targets of these upregulated miRNAs. Downregulated mRNAs were associated with the dysfunction of GABA and dopaminergic synapses, synaptic vesicle recycling, neurotrophin signalling, protein phosphorylation etc. One human postmortem study [24] exhibited the global down regulation of miRNAs in the PFC of the depressed suicide victims. In this case,

many of the significantly down regulated miRNAs were related to cellular growth and differentiation. Owing to their remarkable stability in circulation and as their profile changes significantly under pathological conditions [26], miRNAs have gained support to be considered as reliable biomarkers under disease conditions such as cancer, arterial diseases, neurodegeneration etc. [27-31]. Recently the uses of circulating miRNAs as the biomarkers of MDD has gained importances as a number of studies have showed that specific miRNAs are either overexpressed or expressed in lesser amount in the blood of depression patients compared to control subjects and their expression levels could be corrected to some extent after the treatment with antidepressants [32-34].

### Micro-RNA as a Therapeutic Target for the Treatment of Major Depression

In one study Cho et al. [35] used adipose tissue-derived stem cells (ADSCs), a population of adult stem cells that can self renew and differentiate into multiple lineages. For their miRNA profiling during neurogenesis, they had successfully differentiated these ADSCs into neural cells in vitro in neural induction medium added with hormone, drugs, enzyme inhibitors etc. The successful neurogenesis was confirmed by the presence of many neuron specific markers in the differentiated cells. The workers performed miRNA profiling of undifferentiated and neurally differentiated ADSCs to identify the miRNAs involved in neurogenesis compared to undifferentiated control. Compared to controls, numerous miRNAs exhibited several folds of higher expressions and only a few miRNAs exhibited lower expressions during this process. This study identified numerous miRNAs that were involved in either neurogenesis or glial cell generation as well as the miRNAs involved both in glial and neuron generation. Some top-ranked miRNAs that were involved in neurogenesis were miR-126, miR-373, miR-584, miR-149, miR-191, miR-30c etc. In a different study, Bruno et al. [36] showed that mature miR-128 transcripts were dramatically increased during mice brain development in vivo and during rat neuron maturation in vitro. These phenomena raised the possibility that miR-128 promotes neuron differentiation. To verify this possibility, they used the P19 stem cell line (embryonic carcinoma cell lines derived from an embryo-derived teratocarcinoma in mice), which differentiates into neuron-like cells in response to retinoic acid (RA). They found that undifferentiated P19 cells lacked detectable mature miR-128, but when these cells were induced to differentiate in response to RA, they dramatically upregulated mature miR-128 transcripts. To determine whether the induced miR-128 has a functional role in P19 cells, they transfected them with the sequence-specific miR-128 inhibitor. This inhibitor largely prevented the up regulation of Tuj-1 (Tubb3) and Map2 mRNA (neural markers) and the down regulation of Oct4 mRNA (stem cell marker) in response to RA. These data indicated that miR-128 played a role in promoting gene expression events associated with neural differentiation. To assess whether miR-128 is sufficient to induce neural differentiation, they transfected P19 cells with the miR-128 mimic. This triggered the

same response as that elicited by RA i.e. up regulation of Tuj-1 and Map2 mRNA levels and down regulation of Oct4 mRNA level. Results of the studies performed by Cho et al and Bruno et al indicated that miRNAs which were upregulated during experimental neurogenesis have the therapeutic potential for inducing neurogenesis in the brain.

Till now only one research report is available regarding the miRNA profile in human brain in relation to major depression [24]. In this study miRNA profile was made in the PFC of suicide victims with depression. It was revealed that miRNA expression was globally down regulated in PFC in these subjects compared to control human brains. It was observed that a total of 21 miRNAs were significantly down regulated and many of them had been implicated in growth and differentiation. Among the various mRNA targets of these miRNA several had been correlated with affective disorder that included many brain active transcription factors, splicing factors, several pre- and postsynaptic proteins important for neurotransmission, various signalling proteins, ion channels etc. Comparison of the profile of these down regulated miRNAs with the miRNAs those were up regulated during the neuro-genesis of ADSCs [35], it was deciphered that three down regulated miRNAs in these post-mortem brain samples (hsa-miR-101, hsa-miR-137 and hsa-miR-148b), were substantially up regulated during the neurogenesis of ADSCs. It raised the possibility that these 3 down regulated miRNAs were related to depression due to the lack of neurogenesis activities mediated by them. We speculate that the miRNAs those exhibit their up regulation during experimental neurogenesis can be utilized for therapeutic purposes for depression. As the MDD patients exhibit atrophy and degenerative changes in brain, these miRNA can be delivered in the brain of depression patients to promote neurogenesis and to restore the cognitive functions thereby. There are also miRNAs which were reported to be overexpressed in depression patients. For example, two miRNAs namely- miR-132 and miR-182 those decreases BDNF level in neuronal cell model were found to be expressed at significantly higher level in the circulation of patients with depression than in controls [34].

BDNF is a protein required for neuronal differentiation and survival of neurons [37] and its deficiency in brain is associated with depression [38]. It has been found that the depression patients those exhibited higher expression of miR-132 and miR-182 also exhibited lower serum BDNF levels indicating the involvement of these miRNAs in depression. Thus suppression of the expression of these miRNAs in brain may also be the part of miRNA therapeutics. Alteration of miRNA expressions both in human and in experimental animals implies that that manipulation of miRNA expressions may be an effective treatment for MDD [23,24,25,39]. There are two approaches of miRNA based therapeutics. First, the use of miRNA antagonists which are oligonucleotides having complementary sequence of endogenously upregulated miRNA linked to a disease state. Introduction of this miRNA antagonist in the cell will inhibit the upregulation of disease related miRNA. On the other hand, in the second approach called 'miRNA replacement therapy',

miRNA mimics can be introduced into the diseased and normal cells. miRNA mimics are artificial double stranded miRNA which mimic the downregulated miRNAs that are normally expressed in the healthy cells. As the downregulation of these miRNAs are related to a disease state, introduction of miRNA mimics in patients may restore the normal gene expression [39,40]. In recent times, there is a great enthusiasm regarding use of miRNA as therapeutic targets for treating the diseases like-cancer, myocardial infarction, hepatitis, atherosclerosis, muscular diseases etc. Some miRNAs are at phase II clinical trials and others are under preclinical developments [40,41].

An important difficulty in the delivery of miRNA to the brain is the presence of the blood-brain-barrier (BBB) [42,43]. However, recently some strategies have been made to circumvent this problem. For examples, peptides derived from rabies virus glycoprotein (RVG) carrying antiviral siRNA had been successfully delivered to brain and it afforded robust protection against fatal viral encephalitis in mice [44]. Exosomes are small membranous vesicles secreted by diverse cell types including neurons and have the ability to cross the BBB [45]. Exogenously prepared exosomes containing miRNA have the potential to be developed as CNS therapeutics [46]. For example, intranasally catalase loaded exosome were detected in the brain of Parkinson's disease model mice [47]. Ultrasound in combination with microbubbles have been shown to be useful for the delivery of drugs to brain through transient opening of the BBB. In mice it has been shown that miRNA bearing nanoparticles, which showed enhanced transfection efficiency, could be delivered across BBB to both glial cells and neurons by using focused ultrasound (FUS) and this has shown promise for the treatment of glioblastoma [48].

### Conclusion

In recent times scientists are very optimistic regarding the efficacy of miRNAs as the therapeutic targets for the treatment of many diseases. Many microRNAs are under advanced phase of clinical trials for many deadly diseases like cancer, atherosclerosis, myocardial infarction etc. The main obstacle of microRNA therapy in psychiatric disorders is its delivery to the brain due to the presence of BBB. However, many advances are made in the delivery of this tiny RNA molecule to brain circumventing the obstruction made by BBB. As miRNAs exhibited substantial power of neurogenesis they can be designated as the future molecular medicine of MDD and neurodegenerative disorders.

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