Theranostics of
Brain, Spine & Neural Disorders
ISSN: 2641-8096

Juniper Publishers
key to the Researchers

Short Communication
Volume 1 Issue 5 - August 2017
DOI: 10.19080/TBSND.2017.01.555573

Theranostics of Brain, Spine & Neural Disord

Potential Use of Micro-Rnas as Biomarkers and Therapeutic Purposes in Psychiatric Disorders

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Submission: August 08, 2017; **Published:** August 23, 2017

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Abstract

There is an increasing need of suitable biomarkers for the diagnosis and management of many psychiatric disorders. In recent time, micro-RNAs have shown substantial potential to become the circulatory biomarkers for a number of diseases. In this small review at attempt has been made to acknowledge recent developments in identifying of potential circulatory micro-RNA biomarkers in the diagnosis of some psychiatric disorders. We have also discussed the potential use of micro-RNA for future therapeutic purposes of such diseases.

Keywords: Micro-RNA (mi-RNA); Biomarker; Major depression; Schizophrenia; Therapy

Introduction

Micro-RNAs (mi-RNAs) belong to a class of small RNA molecules comprising of a single strand of 21-23 nucleotides. They are recognized as negative regulators of gene expressions as they suppress the translation by virtue of their ability to bind to 3/ - untranslated region (3/- UTR) of mRNA [1]. Mi-RNAs can also degrade the mRNA by their deadenylation followed by decapping and 5/-3/ decay [2]. It has been estimated that, in human, nearly 30% genes may be regulated by mi-RNAs [3]. Mi-RNAs play major roles in a variety of developmental processes including metabolism, cell proliferation, apoptosis, brain morphogenesis, muscle differentiation etc. [4]. Furthermore, post developmental expressions of mi-RNA are essential for normal physiology and life span [5]. Dysregulations of mi-RNAs i.e. deficiencies or excessiveness have been associated with a variety of diseases like cardiovascular diseases, autoimmune diseases, various forms of cancers, muscular dystrophy, skin diseases, psychiatric disorders and many others [4,6]. Thus overexpression or underexpression of mi-RNA in a particular disease gives rise to signature mi-RNA pattern. As the dysregulation of mi-RNA is associated with many diseases, its modulation through antisense inhibition or replacement may be used for therapeutic purposes [7]. It has been seen that mi-RNA are highly stable in blood as well as under storage and handling conditions [8]. In addition it has been reported that mi-RNA profile is altered in the blood of the patients compared to control subjects. These criteria of mi-RNA has received substantial supports in utilizing its level in circulation as a novel biomarker in many diseases like HIV infection, hepatitis, cancer, renal diseases, cardiovascular diseases etc [9-12]. Recent studies have shown that patients with psychiatric diseases exhibit altered mi-RNA expressions in circulation and brain that can be used as biomarkers of such diseases and also as targets for the treatment.

Mi-Rnas as Biomarkers of Psychiatric Disorders

Dysregulation of mi-RNA biogenesis and mi-RNA target interactions have been related in psychiatric disorders [13]. Neural mi-RNAs are responsive to environmental, synaptic and pathological changes and actively secreted in blood. They are escorted by exosomes that has the ability to cross the blood-brain barrier (BBB) [14]. It has been revealed that circulatory mi-RNA can act as biomarker for many psychiatric diseases like major depression, schizophrenia, bipolar disorder (BD) etc. [15]. In this section we shall make a discussion regarding the efficacies of using mi-RNAs as biomarker for diagnosing some psychiatric disorders.

Major Depressive Disorder (MDD)

In one study circulatory mi-RNA of treatment resistant MDD patients, compared to control subjects, showed the huge reduction of mi-RNAs let-7b and let-7c. Bioinformatics analysis revealed that these two mi-RNAs regulate the expression of many genes in a signaling pathway which is reported to be dysfunctional in depression. The result of this study indicates the suitability of these two mi-RNAs as the biomarkers in depression [16]. In

contrast, in another study, by using quantitative real-time PCR (qPCR), it was observed that plasma levels of a mi-RNA, miR-144-5P was significantly lower in MDD compared to healthy controls. Furthermore, plasma level of the mi-RNA became significantly higher in patients after treatment indicating that this mi-RNA can act as a very useful biomarker in depression [17]. In addition, in another study it was observed that plasma levels of mi-RNAs miR-132 and miR-182 were increased with the simultaneous decrease in the level of brain-derived neurotrophic factor (BDNF) in the patients of depression compared to healthy controls. Bioinformatics study revealed that miR-182 controlled the expression of BDNF [18]. BDNF is involved in cognitive functions like learning [19]. As BDNF activity is reduced in brain of patients of MDD [20] and its plasma level is inversely correlated with miR-182 in depression patients, this mi-RNA also shows promise to be a biomarker for depressive disorder.

Schizophrenia

mi-RNA has received increasing attention in the studies of schizophrenia. Using mi-RNA microarray it has been found in a study that expression of many mi-RNA were dysregulated in prefrontal cortex of the schizophrenia patients in comparison to controls [21]. In a different study [22] plasma level of ten mi-RNAs were analyzed by qPCR in a number of schizophrenia patients. It was observed in that study that mi-RNAs like miR-30e, miR-181b, miR-34a, miR-346, and miR-7 had significantly increased in patients compared to controls. In response to pharmacologic treatments plasma expression levels of miR-181-b and miR-30e were significantly decreased indicating that these mi-RNAs share potentially useful as non-invasive biomarkers schizophrenia diagnosis. The gene encoding miR-346 is located in the intron of a gene which is known to be involved in schizophrenia susceptibility [23] emphasizing the importance of the plasma level of this mi-RNA in schizophrenia diagnosis.

Bipolar disorder (BD)

BD is a heritable psychiatric disorder characterized by recurrent episodes of mania and depression. It has been considered that some of the altered gene expressions in BD may be mediated by the dysregulation of mi-RNAs [24]. In one study [25], by using real-time RT PCR it has been shown that plasma miRNA-134 level was significantly decreased in bipolar mania patients compared to controls and the level was increased following medications reducing the symptoms of mania. The result of this study suggests that decreased circulating miR-134 level is negatively correlated with clinical state of this disease and supports the validity of this miRNA as circulatory biomarker of BD.

The Rapeutic Potential of Mi-RNA in Psychiatric Diseases

Current therapies of psychiatric disorders target several cellular mechanisms such as neurogenesis, enhanced neuroplasticity, calcium regulation, cell survival and many others. From therapeutic point of view mi-RNAs provide great advantages as they are able to target numerous genes that could be involved in these processes [26]. Mi-RNA dysregulation i.e. both their increase and decrease are associated with pathophysiologies of psychiatric disorders [27]. As the circulatory mi-RNA may correlate the mi-RNA changes in the brain [28] it can be speculated that appropriate mi-RNA delivery to brain can mitigate the symptoms of psychiatric disorders. Use of antisense can selectively suppress the pathologically abundant mi-RNA. In contrast, reduction of useful mi-RNAs, that lead to excessive translation of target mRNA that negatively affect the neuronal physiology, can be supplemented by the introduction of mi-RNA mimics in the brain [29].

Delivery of mi-RNA to brain is problematic due to the presence of BBB. In spite of this challenge researches are focused for using mi-RNA as therapeutic for psychiatric disorders. For example, Adeno-associated viruses (AAV) have shown to be a safe and effective mean of gene delivery [30]. Exosomes are small membranous vesicles secreted by diverse cell types including neurons and have the ability to cross the BBB [31]. Exogenously prepared exosomes containing mi-RNA have the potential as candidate CNS therapeutics [32]. Furthermore, peptide derived from rabies virus glycoprotein (RVG) carrying antiviral siRNA successfully delivered to brain and provided protection against fatal viral encephalitis in mice [33]. From these instances it seems possible that mi-RNA therapy can provide more specific treatments for psychiatric disorders.

Conclusion

From the aforesaid discussions it appears that circulatory mi-RNAs can be used as biomarkers for psychiatric diseases. They also give us hopes for its use in more specific treatments of such diseases in future.

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How to cite this article: Ashim K B, Tridip C. Potential Use of Micro-Rnas as Biomarkers and Therapeutic Purposes in Psychiatric Disorders. Theranostics of Brain, Spine & Neural Disord. 2017; 1(5): 555573. DOI: 10.19080/TBSND.2017.01.555573

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DOI: 10.19080/TBSND.2017.01.555573

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