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Review Article

The Potential Role of miRNAs in Schizophrenia: Diagnostic and Therapeutic Applications

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Abstract

Schizophrenia is a severe mental disorder which affects the normal functioning of the brain. To date, the etiology of schizophrenia is unclear; therefore, the diagnosis of schizophrenia is controversial. Biomarkers that reflect the dysregulations observed in schizophrenia may potentially assist the diagnosis of the disorder. Given the critical need for new diagnostic markers and disease-modifying treatments, expanding the focus of genomic studies of neuropsychiatric disorders to include the role of non-coding RNAs is of growing interest. MicroRNAs small non-coding RNA transcripts expressed throughout the brain that can regulate neuronal gene expression at the post- transcriptional level. Dysregulation or altered expression of miRNAs is associated with abnormal brain development and pathogenesis of neurodevelopmental diseases. This review highlights the potential of miRNA levels to be used in the diagnosis of psychiatric disorders and offer novel targets for therapeutic development.

Keywords: *Biomarker; miRNA; ncRNA; Neuropsychiatric Disorder; Schizophrenia*

Abbreviations

Ago2: Argonaute 2; CNS: Central Nervous System; DGCR8: Digeorge Syndrome Critical Region Gene 8; DLPFC: Dorsolateral Prefrontal Cortex; NSCs: Neural Stem Cells; PBMCs: Peripheral Blood Mononuclear Cells PBMCs; PFC: Prefrontal Cortex; RAN: RAs-Related Nuclear Protein; RISC: RNA Induced Silencing Complex; SCZ: Schizophrenia; SNPs: Single Nucleotide Polymorphisms; TRBP: Transactivating Response RNA-Binding Protein

Introduction

Schizophrenia (SCZ) is a debilitating psychotic disorder characterized by a diverse range of symptoms and cognitive impairments. While the neuropathology is relatively subtle and inconsistent at the anatomical, cellular and molecular levels; advances in neural imaging and histological techniques are refining our understanding of the spectrum of changes in gross anatomy, neural circuitry and cytoarchitecture. In recent years, the molecular neuropathology has also been developed by the advance of high- throughput genomics and proteomics [1]. These permit a systems-level methodology to understanding the role of molecular networks and interaction rather than individual candidate genes. In terms of etiology and pathophysiology, it is not only a genetically defined disorder but also an environmentally induced dynamic process comprising dysregulation of numerous pathways [2]. The genetic contribution is important, since SCZ has been revealed to have a heritability risk of ~60% suggesting a much greater role of the environment SCZ development [3].

Several studies propose that defective neuronal plasticity and function in neurodevelopmental disorders may have caused from diminished post-transcriptional regulation mediated by microRNAs (miRNAs) [4]. Accumulative evidences suggest that miRNAs play significant roles in the etiology of neuropsychiatric, neurodevelopmental disorders, and neurodegenerative diseases [5].

The discovery of small regulatory miRNAs has entirely changed our understanding towards gene regulatory mechanisms which were mostly thought to be governed by elements such as operators, promoters, transcription factors such as inducers and repressors, epigenetic factors (DNA methylation, histone acetylation), alternate splicing and post-translational modifications. miRNAs are small (~22 nucleotides long), ncRNAs that regulator the expression of target transcripts by perfect or imperfect complementary binding and inducing either mRNA degradation or translational repression [5]. These small RNAs have appeared as novel regulators of gene expression in almost all vertebrate species. They are believed to post-transcriptionally control ~60% of human genes including transcription factors [6]. Extensive research has been done on the role of miRNAs in normal and pathological conditions in human and animal models [7,8] and current research has emphasized their importance in SCZ [9,10].

This review highlights the potential of miRNA levels to be used in the diagnosis of SCZ and discuss the potential clinical utility of miRNA as novel biological markers and therapeutic targets for SCZ.

miRNA Biogenesis and Function

An outline of the steps involved in miRNA biogenesis is demonstrated in figure 1. The biogenesis of miRNAs starts with the spirit of the promising primary miRNA transcript (pri-miRNA) that can measure up to several thousands of nucleotides and contain stem-loop structures. These pri-miRNA are, for the largest part, transcribed by RNA polymerase II [11]. About 50% of miRNAs have their own promoter. The other half can be found in intronic or exonic regions of coding or non-coding transcription units. Once the pri-miRNA is synthesized, it is cleaved and a small hairpin structure that is termed pre-miRNA is released. This reaction takes place in the nucleus and is accomplished by the nuclear RNAse III-type protein Drosha. This maturation process involves the participation of a cofactor, the DiGeorge syndrome critical region gene 8 (DGCR8). Along with Drosha, DGCR8 forms a large complex that is called the Microprocessor [12]. Regardless of the sequences of the pri-miRNAs, the Microprocessor complex cleaves the pri-miRNA into a ~70 nucleotide pre-miRNA, generating an imperfect stem-loop structure. The efficiency of miRNA precursor recognition and processing by Drosha depends on the terminal loop size, the stem structure and the flanking sequences of Drosha cleavage sites [13]. It should be noted that intronic pri-miRNAs termed mirtron, can bypass the Microprocessor [14]. Instead, these precursors use classic splicing machinery and do not necessitate Drosha cleavage [15].

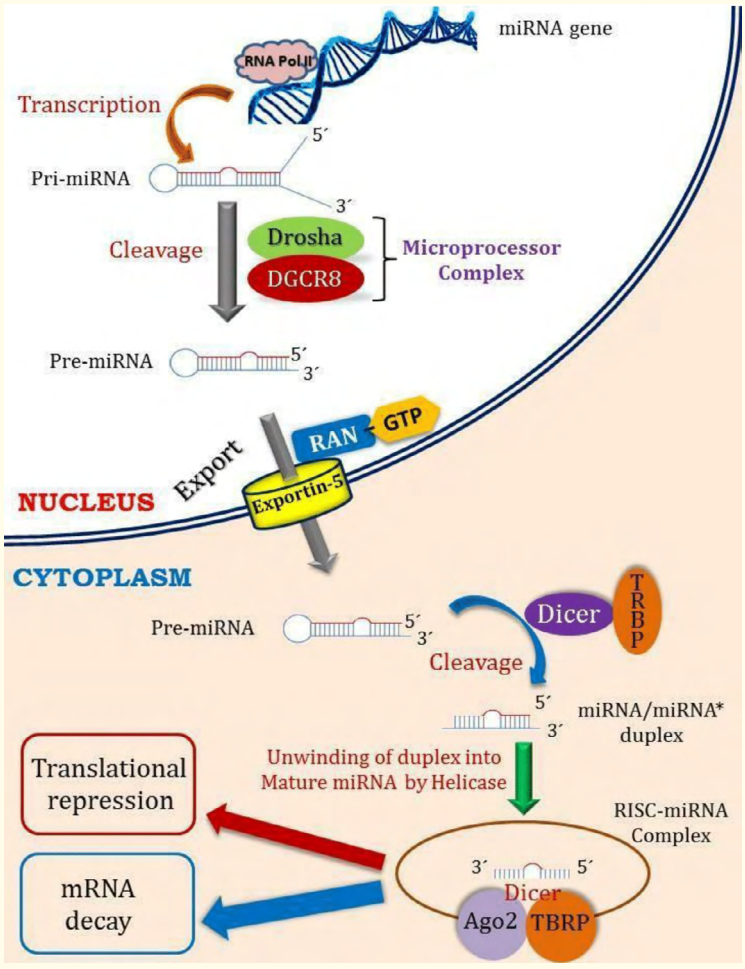

Figure 1: *The miRNA processing typically starts with transcription of the pri-miRNA by the RNA polymerase II or III and followed by the cleavage of this primary transcript into a pre-miRNA by a complex formed of Drosha and DGCR8, termed the Microprocessor. The next step involves the RAN-GTP dependent Exportin-5 that allows nuclear export of the pre-miRNA. This new localization permits the RNase Dicer and the double-stranded RNA- binding protein TRBP to cleave the pre-miRNA, thus making an imperfect duplex of about 22 nucleotides in length with 2 nucleotides 3′ overhang. Argonaute 2 (Ago2), based on thermodynamic rules, will then choice the suitable strand, leading to RNA-induced silencing Complex (RISC) formation and regulation of specific mRNAs.*

The next step involves Exportin-5, a RAN-GTP dependent nucleo/cytoplasmic cargo transporter that exports pre-miRNAs out of the nucleus to the cytoplasm. This alteration in cellular localization permits Dicer, a type-III RNAse, to cleave the hairpin precursors into a small double stranded RNA (dsRNA) duplex that contains both the mature miRNA strand and its complementary strand. The subsequent processing reaction contains the Transactivating response RNA-Binding Protein (TRBP) that binds the miRNA duplex via its dsRNA binding domain. TRBP then recruits Argonaute2 (Ago2), which is the major component of the RISC complex (RNA Induced Silencing Complex) [16] (Figure 1). The role of the RISC complex is to select and recruit the RNA strand that has the lowest thermodynamic stability at its 5′-end (termed the guide strand). The complementary strand is more likely to be degraded as it is excluded from the RISC complex [17].

This miRNA controlling machinery is emerging as a key control system in all biological processes including the complex central nervous system (CNS) processes during embryonic development, growth, aging and neurodegenerative diseases. Proper functioning of these cellular events require well-coordinated gene expression and regulation program. Accumulative evidence suggests that miRNAs regulator the post- transcriptional processes to control gene expression during neuronal activity [18]. Specific miRNAs have been associated in neuronal differentiation and maintenance of neuronal phenotype. For example, miR-133b is augmented in midbrain dopamine neurons of the mammalian brain where it controls the maturation and function of midbrain dopamine neurons through a negative feedback circuit containing the transcription factor Pituitary homeobox 3 (Pitx3) [19]. The brain-enriched miRNA, miR-124, stimulates neuronal gene expression in differentiating neural progenitor cells(NPCs) [20]. As many miRNAs have been described to extensively involve in CNS activities, we speculate that any disruption in their activity/function may lead to a wide range of CNS abnormalities, including brain aging.

Function of miRNAs in the Central Nervous System

The CNS composed mainly by neurons and accessory-maintenance cells called glial cells, denotes one of the most complex structures in an organism. Functions of the CNS comprise receiving, integrating, conducting, and responding to environmental stimuli, accomplished by the neuronal networks residing in the brain [21]. During development, most of the cells within the CNS are produced from pluripotent stem cells precursors. This procedure includes the generation of more specialized multipotent cells called neural stem cells (NSCs). According to their brain origin, NSCs are then devoted to form neural progenitors, which are lineage-specific cells that, depending on numerous external and internal fine-tuned signals, will discriminate into particular cell types such as neurons or glial cells. Thus, the appropriate functioning of the CNS relies on accurate cell differentiation, which needs a coordinated program of positive and negative signals to control gene expression in a suitable manner through different cellular stages that range from NSCs to terminally differentiated cells [22]. Neurogenesis, for example, involves a precise and controlled program of gene expression that depends on regulatory feedback loops to confirm the precise pattern of gene expression to make a proper cell type in a precise spatiotemporal window [22,23]. As shown in the following examples, miRNAs have an active regulatory role through each stage of neural differentiation. The key role of miRNAs in development of the CNS is further highlighted by the fact that miRNAs have a cross-species conserved function and display tissue- and cell type- specific expression profiles during CNS development [24]. This makes them attractive regulators of gene expression during the cell differentiation process.

Numerous examples of the participation of specific miRNAs during the establishment of NSCs and NPCs have also been described. *let-7* and miR-125b were displayed to induce neuronal lineage commitment in mouse and human cells, respectively [25,26]. miR-9a is very well conserved among fish, chicken, and mouse, and its expression in these organisms has been identified exclusively in NPCs. Moreover, miR-9a plays a significant role during the establishment of the midbrain- hindbrain boundary in vertebrates by targeting the anti-neurogenic genes *her5* and *her9* [27].

Moreover, miRNAs are involved in the establishment of precise neural phenotypes. miR-124 for example is expressed exclusively in neurons, whereas miR-92b has been found only in neuronal progenitors [23]. miR-124 is the most abundant miRNA within the CNS, and it is conserved from nematodes to primates. miR-124 is able to induce a neuronal phenotype when overexpressed in embryonic stem cells

[28]. miR-124 also regulates the transition from neural progenitor to mature neuron by constraining nonneuronal genes (scp1 and sox9) [20,29] and the polypyrimidine tract-binding protein1 (Ptbp1 or Ptb), an anti-neuronal factor that regulates negatively neuron specific alternative splicing [29]. This discovery discloses that the regulation employed by miR-124 on its different target genes is crucial for neuronal differentiation and lineage commitment.

Additional examples are miR-129, miR155, and miR122. These miRNAs are able to constrain bipolar neuron regeneration in the Xenopus retina through the downregulation of otx2 and vsx1, which positively regulate the commitment of progenitor cells to bipolar cells [23].

miRNAs not only regulate neural functions but also other brain cells. A key signal for the attainment of a glial cell fate is the phosphorylation of the signal transducer and activator of transcription 3 (Stat3). As said, miR-9 and miR-124 are considered by their participation in the determination of a neuronal cell fate. By overexpressing these two miRNAs, the levels of phosphorylated Stat3 decrease, so the rate of glial cell fate determination is reduced [30]. Although the goal for these miRNAs has not been recognized, one could envisage that both might control the levels of a specific kinase or a phosphatase inhibitor involved in Stat3 phosphorylation. Thus, it is clear that the communication between different miRNAs and signaling pathways pays to determine precise cell fates.

Assumed their ubiquitous functions, it is not surprising that miRNAs are involved in all stages during CNS development. Although far from being extensive, the examples given above may help us to produce a hypothetical overview of the miRNAs function during CNS differentiation process: in renewing NSC, miRNAs will tend to silence prodifferentiation genes as well as to repress negative regulators of proliferative genes. As differentiation goes on, the miRNA expression profile may change, and miRNAs that target renewal and proliferative genes may be expressed. During terminal phases of differentiation, miRNAs should silence several nonneuronal or nonglial genes and suppress genes involved in cell cycle progression (in the particular case of neurons) while permitting the expression of particular neuron or glial specific markers, giving the cell a definite identity. All these processes should control and continually be regulated by various signaling pathways as well as epigenetic mechanisms, both fundamental processes during differentiation.

miRNAs in Schizophrenia

SCZ is a devastating psychiatric disorder that has a lifetime prevalence of ~1% in most of the populations studied and is characterized by impaired cognition, positive psychotic symptoms such as hallucinations, delusions, and disorganized behavior, as well as negative symptoms such as social withdrawal and apathy.

Although SCZ is considered mostly heritable, with an estimated rate of heritability about 80%, the effect of susceptibility genes has been small [31]. Because miRNAs play crucial roles in brain development and have the ability to target numerous genes, the potential roles for miRNAs in the abnormal brain development in SCZ have been studied [32] (Table 1). The strongest line of indication for a direct pathogenic link between SCZ and miRNA biogenesis is provided by Stark and colleagues using a mouse model of the 22q11.2 microdeletion, one of the highest known risk factors for SCZ 33]. A „hot spot" for neuropsychiatric disorders, including SCZ, has also been defined on chromosome 8. This area comprises numerous miRNAs, advancing support to their role in SCZ [34].

Sample Type	Analysis	miRNA	References
Postmortem tissue - parietal cortex (BA7)	Microarray	No significant difference in miR-130b	[62]
Postmortem tissue - PFC (BA9)	Microarray qRT-PCR	**Up-regulation:** miR-106b **Down-regulation:** miR-26b, miR-30b, miR-29b, miR-195, miR-92, miR-30a-5p, miR-30d, miR-20b, miR-29c, miR-29a, miR-212, miR-7, miR-24, miR-30e, miR-9-3p	[42]
Postmortem tissue – superior temporal gyrus (BA22)	Microarray	**Up-regulation:** miR-181b	[63]
PFC	Microarray qRT-PCR	**Down-regulation:** miR-219	[39]
Postmortem tissue – frontal cortex (BA10)	Microarray qRT-PCR	**Down-regulation:** miR-30e, miR-195	[64]
Postmortem tissue – DLPFC (BA46)	Microarray qRT-PCR	**Down-regulation:** miR-346	[3]
Postmortem tissue - superior temporal gyrus (BA22) and DLPFC (BA9)	Microarray qRT-PCR	**STG and DLPFC: Up-regulation:** DGCR8 (miRNA biogenesis gene), miR-107, miR-15 family members (miR-15a/b, miR-16 and miR-195), miR-181b, let-7e **STG: Up-regulation:** miR-20a, miR-26b DLPFC: Up-regulation: miR-128a, miR-16, miR-181a, miR-20a, miR-219, miR-27a, miR- 29c, miR-7, miR-19a, miR-26b, let-7d	[65]
Postmortem tissue – DLPFC (BA46)	Microarray qRT-PCR	**Up-regulation:** miR-34a, miR-132/132*, miR-212, miR-544, miR-7, miR-154*	[35]
Postmortem tissue - PFC (BA9)	qRT-PCR	**Up-regulation:** miR-193b, miR-545, miR-301, miR-27b, miR- 148b, miR-639, miR-186, miR-99a, miR-190 **Down-regulation:** miR-33, miR-138, miR-151, miR-210, miR- 324-3p, miR-22, miR-425, miR-106b, miR-338, miR-15a, miR-339	[66]
Postmortem tissue - DLPFC (BA46)	Microarray qRT-PCR	**Up-regulation:** Confirmed by qPCR: Dicer (miRNA biogenesis gene), miR-17, miR-107, miR-134, miR-150, miR-199a*, miR-25, miR-328, miR-382, miR-487a, miR-652	[67]
Peripheral tissue (WBCs)	TaqMan Low Density Array v.1.0	**Up-regulation:** miR-34a, miR-449a, miR-548d, miR-564, miR-572, miR-652 **Down-regulation:** miR-432	[44]
Peripheral tissue (PBMC)	Microarray qRT-PCR	**Down-regulation:** miR-107, miR-1275, miR-128, miR-130b*, miR-134, miR-148b, miR-150*, miR-151-3p, miR-16-2*, miR-181a, miR-200c, miR-224, miR-28-3p, miR-28-5p, miR-29b-1*, miR-30e*, miR-31, miR-329, miR-335*, miR-342-5p, miR-409-3p, miR-431, miR-432, miR-486-3p, miR-487b, miR-544, miR-574-3p, miR-576-5p, miR-584, miR-625*, miR-664, miR-877, miR-9	[45]
Human and Mouse Postmortem tissue - DLPFC (BA46)	Microarray	**Up-regulation, uncorrected p-value:** miR-320, miR-320c, miR- 628-3p, miR-874, miR-105, miR-17*, let-7b **Down-regulation, corrected p-value:** miR-132, miR-132* **Down-regulation, uncorrected p-value:** miR-150, miR-133a	[40]
Peripheral tissue (Serum)	qRT-PCR	**Up-regulation:** let-7g, miR-181b, miR-219-2-3p, miR-1308 **Down-regulation:** miR-195	[46]
Postmortem tissue - DLPFC	Microarray qRT-PCR	**Up-regulation:** miR-17	[68]
Postmortem tissue - laser- captured parvalbumin- immunoreactive neurons from layer 3 of STG (Brodmann's area 42)	Megaplex miRNA TaqMan Arrays	**Up-regulation:** miR-151, miR-338-5p, miR-197, miR-342, miR- 518f, miR-1274b, miR-151-3p, miR-197, miR-34a, miR-520c-3p **Down-regulation:** miR-106a, miR-218, miR-342	[69]
Postmortem tissue - DLPFC	qRT-PCR	**Up-regulation:** miR-17-5p, miR-18a, miR-106a, miR-106b, miR- 590-5p	[70]
Peripheral tissue (PBMC)	Microarray	**Down-regulation:** miR-132, miR-134, miR-1271, miR-664*, miR-200c, miR-432	[71]
Peripheral blood sample	qRT-PCR	**Up-regulation: miR-124-3p**	[72]
Hippocampal neuronal cultures		**Up-regulation: miR-214**	[9]
Peripheral tissue (Plasma)	qRT-PCR	**Up-regulation: miR9-5p, miR-29a-3p, miR106b-5p, miR125a-3p, miR125b-3p**	[47]
Peripheral tissue (Serum)	Microarray qRT-PCR	**Down-regulation: miR-21**	[48]
Peripheral blood sample	qRT-PCR	**Up-regulation: miR-137**	[73]
Leukocytes	Illumina HiSeq Sequencing	**Down-regulation: miR-941**	[74]

Table 1: *Studies of miRNAs in SCZ.*

DLPFC: Dorsolateral Prefrontal Cortex; PBMC: Peripheral Blood Mononuclear Cell; PFC: Prefrontal Cortex; WBCs: White Blood Cells

In most of the miRNA profiling studies, postmortem brain tissues from SCZ patients are used, and an enormous number of differentially expressed miRNAs have been recognized [35-38] (Table 1). Some of these dysregulated miRNAs could modulate the expression of genes associated with SCZ [39,40]. Early studies on postmortem brains revealed an overall decrease in miRNA expression in the prefrontal cortex (PFC) of SCZ patients [41,42]. These miRNAs include miR-26b, miR-29b, miR-30b, and miR-106b. A following independent study presented that the expression of miR-132 and miR-132* was significantly reduced in brains of SCZ patients [40]. miR-132 has been shown to potentiate N-methyl-D-aspartate (NMDA) receptor depolarization [43]. The reduced expression of miR-132 in SCZ patients is consistent with the hypofunction of the NMDA receptor in SCZ patients.

Analysis of miRNA expression in peripheral tissues has also discovered associations with SCZ. Lai and colleagues found 6 upregulated miRNAs and 1 downregulated miRNA in the white blood cells of SCZ patients compared to healthy controls [44]. In another study, Gardiner and collaborators identified 7 downregulated miRNAs in peripheral blood mononuclear cells (PBMCs) of SCZ patients [45]. Shi and colleagues also analyzed miRNA expression in the serum of SCZ patients, and observed 4 upregulated miRNAs whereas one miRNA was downregulated [46]. Recently, Camkurt and colleagues found 5 microRNAs that were upregulated in the plasma of SCZ patients. These microRNAs are predicted to be targeting important genes for SCZ [47]. In an another study, global plasma miRNAs were profiled in an initial discovery cohort of 164 SCZ patients and 187 controls followed by replication in a cohort of 400 SCZ patients, 213 controls, and 162 non-SCZ psychiatric patients, and miR-130b and miR-193a-3p levels are upregulated in SCZ but not controls or other psychiatric disorders [10].

Given the effect of antipsychotics on gene expression, growing consideration has been given to alterations in miRNA expression levels following antipsychotic medication in the treatment of SCZ. Recent study suggested that the therapeutic action of antipsychotic treatment in patients with SCZ is correlated with a significant reduction in PBMC miR-21 expression levels and that antipsychotics play a significant role in improving symptoms and in simultaneously restoring overexpressed plasma miR-21 [48]. Similarly, few studies that examine circulating miRNAs and their response to antipsychotic medication in SCZs have been published [40,49,50]. Liu., *et al*. found miR-365 and miR-520c-3p expression levels were significantly reduced in plasma after risperidone treatment in SCZ, which revealed that circulating miRNAs respond to antipsychotic monotherapy in fist-episode SCZ with remission [49].

In addition to the changes in miRNA expression in SCZ an increasing number of genetic studies has provided exciting links between miRNAs and SCZ. Initially, single nucleotide polymorphisms (SNPs) within miR-206 and miR-198 were presented to be nominally related with SCZ [51]. Additionally, another SNP in pre-miR-30e was strongly associated to the disease [52]. Furthermore, different SNPs (rs1625579; rs1198588, rs1702294) in the upstream region of the host gene for miR-137 have been strongly related with SCZ [53-55].

Environmental factors can also impact miRNA levels and have inferences for SCZ. For instance, maternal immune activation (MIA) in animals using polyriboinosinic- polyribocytidilic acid (poly-I:C) is an important tool for studying the role of maternal infections in pathophysiology of SCZ and causes phenotypic aberrations in the progeny that mimic SCZ. Hollins and colleagues identified 21 miRNA species that were differentially expressed after MIA treatment in rats [56]. Finally, a two-hit model in which poly-I:C-affected rats were exposed to HU210 during adolescence produced 18 differentially expressed miRNA species. Target forecast of these 18 miRNAs have shown potential roles in mitogen-activated protein kinase signaling, essential for neuronal development and cognition [57], and the Wnt signaling pathway, also important in neuronal development and SCZ [58]. This study highlights the ability of environmental factors to influence miRNA expression, which may have a role to play in the etiology of SCZ.

miRNAs as a Potential Biomarkers in Schizophrenia

Biomarkers are valuable tools to diagnose individuals at the early stages of disease, to develop therapeutic strategies, and to provide prognostic information. Presently, diagnosis of neuropsychiatric disorders relies on behavioral and clinical symptoms, which appear after several years of disease progression. Thus, establishment of biomarkers that permits early detection is of utmost importance for the management of these disorders [2]. miRNAs not only can be employed for monitoring treatment but also promising prognostic biomarkers for predicting drug response. The finding of the role of miRNAs in drug resistance and drug response can potentially progress diagnosis, treatment and prognosis in patients.

In the perspective of SCZ treatment, Wei and colleagues recognized two upregulated miRNAs (miR-130b and miR-193a-3p) in the plasma of SCZ patients, which were repressed in remitted patients after one year of treatment with antipsychotic drugs (aripiprazole and risperidone) [10]. The baseline levels of these two miRNAs were lower in patients in remission, compared to patients who were not

in remission. Thus, their results propose that miR-130b and miR-193a-3p levels can be used as potential biomarkers to forecast drug response in SCZ patients. Gardiner and colleagues examined the expression profile of miRNA in PBMCs of 112 patients with SCZ and 76 non-psychiatric controls [45]. The authors identified 83 miRNAs that were significantly downregulated in the schizoaffective group, including a large subgroup of miRNAs (20%) transcribed from a single engraved locus at the maternally expressed DLK1-DIO3 region on chromosome 14q32. Remarkably, miR-449a was shown to be closely related with the majority of features studied in the Wisconsin Card Sorting Test [59], representing the likely participation of miR-449a in the executive function of the brain [60]. Both of these studies have recognized peripheral patterns of miRNA that could have utility as biomarkers for SCZ and related sub-phenotypes. Though, as most of the subjects stated the use of medication and some exposure to drugs and alcohol, larger studies with more comprehensive examination of these confounds are required to outline their influence on miRNA expression in this tissue.

With the identification of miRNA biomarkers in peripheral tissues, the clinical expansion of miRNA oriented pharmaceutical interferences may be convoyed by miRNA-based clinical diagnostics. New biomarkers for SCZ and related phenotypes could finally offer the basis for earlier detection, disease stratification and the forecast of response to drugs and side effects. Assembly a better gratitude of the role of miRNA in the brain and in neuropsychiatric disorders such as SCZ is a massive challenge, but the potential significance of these discoveries are likely to be highly significant.

Therapeutic Applications and Challenges

SCZ has an intricate neurobehavioural phenotype that is supposed to develop through disturbances in neural circuitry and synaptic function [61]. The complex mechanism and architecture of synapses in the human brain involves coordination of a similarly intricate intracellular network of molecular signal transduction systems. The redundancy of these networks means that numerous combinations of gene variants can give rise to system dysfunction that manifest as associated neurobehavioural syndromes. Post-transcriptional gene regulation and small ncRNA are likely to be key factors shaping the topography of this matrix. This review summarized the involvement of miRNAs in SCZ with different levels of evidence.

The expression of miRNAs is dysregulated in the brain of SCZ patient compared to the healthy controls. The genetic evidence has displayed that mutations that interrupt miRNA transcription were found in SCZ. Precise function of specific miRNA has been revealed to be associated with SCZ. Furthermore, the manipulation of miRNAs expression could change the phenotypes in SCZ using animal model. These model systems not only provide the basis for understanding the phenotype of miRNA dysfunction, they provide a platform for the exploring therapeutics. miRNA and the fundamental miRNA biogenesis machinery are potentially both novel drug targets and new drug entities in the fight to control neuropsychiatric conditions.

Besides using miRNA as a target, the upstream controller of miRNAs could also be the object of potential manipulation. However, which one is more effective needs to be further assessed. Further, due to blood brain barrier (BBB), it may be difficult to attain specific delivery of miRNA to its envisioned target. Finally, the synthetic technology and deliver technology are also aspects that should be taken into consideration. We believe with the rapid advances in systematic drug delivery, successful miRNA-based therapeutics in SCZ will be accomplished in the near future.

Conclusion

The discovery and development of miRNA-based therapeutics, as well as the various ranges of molecular cascades they can control, offer a new approach for treating diseases with a heterogenetic or epigenetic origin. To date, miRNAs extracted from brain tissue, cerebrospinal fluid and PBMCs have been used as biomarkers in the diagnosis of SCZ; furthermore, the deciphering of the miRNA genome may contribute to elucidating the etiology and improving the treatment of SCZ. miRNAs extracted from other peripheral sources, however, have not been examined. Forthcoming studies should examine miRNAs from other peripheral fluids, including saliva and urine, as these may also be potential biomarkers in the diagnosis of SCZ.

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I would like to declare that there is no conflict with other interests.

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