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DEREGULATED MICRORNA EXPRESSION IN BIOSPECIMENS FROM PATIENTS DIAGNOSED WITH SCHIZOPHRENIA AND BIPOLAR DISORDER AS A DISEASE BIOMARKER

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Abstract

The biological markers for schizophrenia (SZ) and bipolar disorder (BD) would represent a precious tool in evaluating the risk for the development of these common neuropsychiatric diseases and, possibly, in the prevention of either disease episodes and/or treatment efficiency monitoring. Since both SZ and BD are diseases with a significant genetic component, the research over the last decades has focused on the genes with altered function in the central nervous system (CNS) of individuals suffering from these illnesses. Recently, however, small non-coding RNA molecules (microRNAs, miRNAs, miRs) were shown to regulate the expression of human CNS genes involved in cell processes and functions negatively affected in neuropsychiatric disorders, including synaptic development and maturation, learning and memory. Differentially expressed sets of miRNAs have been reported in the tissues of SZ and BD patients in comparison to controls suggesting the emergence of a novel class of potential biomarkers. Here we review the reports on the changes in miRNA expression in postmortem brain tissue and peripheral blood in SZ and BD. We also evaluate the potential of miRNA packaged in exosomes, signaling vesicles released by neurons and glia, to contribute to the disaggregation of the molecular machinery underlying mental disorders and provide clinically useful biomarkers.

Keywords

• Biomarker • Bipolar disorder • MicroRNA • Schizophrenia

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Introduction

Schizophrenia (SZ) and bipolar disorder (BD) are common diseases with poorly understood pathophysiology, diminished quality of life and reduced lifespan. According to the National Institute of Mental Health, it is estimated that 51 million people worldwide suffer from SZ [1]. BD has a lifetime risk estimated as high as 4%, accompanied by a 20% lifetime suicide risk [2,3]. Both SZ and BD are highly heritable, polygenic diseases [4,5], making candidate genes elusive. Additional confounding factors in the quest for SZ and BD genes are clinical heterogeneity and phenotypic and genetic overlaps with other mental illnesses [6-9]. MicroRNAs, molecules that up- or down-regulate the translation of messenger RNA (mRNA) or render it unstable, regulate neuronal functions [10] and cognitive performance [11]. Lines of evidence accumulated to support involvement of miRNA in the pathophysiology and pharmacotherapy of neuropsychiatric diseases have been recently reviewed [12].

Here we focus on microRNA expression studies in SZ and BD tissues. We also discuss the potential of miRNAs packaged into exosomes to provide insight into disease pathogenesis and/or represent a disease biomarker - a read-out of specific changes in a multifaceted system. Exosomes are a well-characterized category of secretory vesicles, defined by size (30-90 nm), buoyant density (~1.1-1.2 g/ml), lipid composition and the presence as well as the absence of specific marker proteins [13]. Because of the specific molecules on their surface, including cell-adhesion proteins, exosomes can be incorporated by specific recipient cells [14,15]. Oligodendrocytes, astrocytes and neurons release exosomes [13,16-22] - microvesicles that shuttle proteins and genetic materials including miRNAs [23] that can alter the proteome of the recipient cell [24-28]. The rationale for studying exosomal rather than whole tissue miRNA stems from the recently accumulated evidence for the role of exosomes in cell-signaling [29-32] and their potential to serve as a diagnostic tool [33].

Deregulation of miRNA expression in postmortem cortex in SZ and BD

Several studies applied microarray, followed by qualitative reverse transcription-PCR on human postmortem dorsolateral prefrontal cortex (DLPFC) and/or superior temporal gyrus of patients diagnosed with SZ or BD and of control subjects [34-39]. These studies, while relatively similar in number of specimens (~20-40 subjects in each category) and in number of miRNAs examined in microarray (mostly ~300-400, occasionally more, up to ~850), resulted in few overlapping findings. To validate the microarray findings, qPCR analyses confirmed relatively small portions of differentially expressed miRNAs in microarray experiments diminishing further the number of miRNAs consistently miss-expressed in the cortices of SZ and BD patients.

A recent study, rather than examining microRNA isolated from the whole tissue, compared miRNA expression in exosomes extracted from DLPFC of patients diagnosed

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with SZ or BD or non-psychiatric controls [40]. The top two differentially expressed (upregulated) miRNAs in DLPFC- derived exosomes of SZ patients according to microarray were miR-31 and miR-33 [40]. miR-33 was previously reported among miss-expressed (downregulated) miRNAs in DLPFCs of both SZ and BD individuals [39]. Three more miRNAs from top-ranked differentially expressed (upregulated) DLPFC exosomal miRNAs by Significance of Microarray Analysis (SAM) [40] were on the list of significantly down-regulated miRNAs in SZ by Perkins and colleagues [34]: miR-92, -20b, and -30e. miR-92 and -20b belong to miR-17-92 cluster known to be a potent oncogene [41]. miR-17 has been suggested to regulate NPAS3, a developmentally important transcription factor implicated in the pathogenesis of SZ [42]. Increased miR-17-5p expression has been reported in DLPFC in SZ [35]. Potentially pertinent for SZ pathobiology, miR-92 was shown to developmentally regulate neuronal K(+)Cl(-) co-transporter 2 (KCC2), a modulator of GABA effects [43]. Moreover, miR-92a was slightly down-regulated in the sera of SZ patients in comparison to controls [44]. Finally, down-regulation of miR-30 may be important for neuronal survival [45].

While qPCR analysis in DLPFC derived exosomes was technically successful for only a limited number of miRNAs differentially expressed in SZ and BD samples according to SAM, it did establish a significantly increased miR-497 expression in SZ patients [40]. miR-497 together with miR-195 – one of few miRs previously reported differentially expressed in the cortices of SZ subjects (DLPFC [34] and superior temporal gyrus, STG [36]) belong to the well-studied miR-15/107 family implicated in the pathogenesis of neoplasms, neurodegenerative diseases and heart disease [46]. The family members miR-15a, miR-15b, and miR-16 have been reported as significantly up-regulated in both DLPFC and STG of SZ patients [36]. Additional miRs from the same family have been reported as miss-expressed in both cortices and peripheral blood mononuclear cells (PBMCs) of SZ patients (miR-107 [35,36,47]) or in sera (miR-103 [44]).

Like miR-497, miR-29c was among top differentially expressed miRs in DLPFC exosomes in both SZ and BD according to SAM [40]. miR-29c was significantly up-regulated in SZ DLPFC tissue also in the study by Beveridge *et al.* [36], and, in the same fashion, together with miR-29b, in the study by Perkins *et al.* [34]. However, qPCR analysis in DLPFC exosomes of SZ, BD, and control subjects, demonstrated significantly increased expression only in BD samples [40]. This is intriguing because miR-29c is induced by canonical Wnt signaling [48] that is antagonized by GSK-3, a known substrate of inhibition by lithium, a first line of therapy for BD [49]. Interestingly, the direction of a change in expression (up- or down- regulation) for miRNAs deregulated in psychosis, either an individual or a set of miRs, has been shown to vary substantially among studies (e.g. miR-15 [36,39] or the majority of miRs examined [34,35]). In addition, even within a same study, a miss-expressed miR in SZ or BD may be down-regulated in a microarray and up-regulated in the subsequent qPCR analysis [34,40]. In the study by Banigan *et al.* these changes were attributed to a different set of control samples used in microarray vs. qPCR experiment [40].

Deregulation of miRNA expression in peripheral blood mononuclear cells (PBMCs) and plasma in SZ and BD

Two studies evaluated miRNA expression in PBMCs in search for SZ biomarkers with no overlapping findings [47,50]. However, the study by Gardiner *et al.* [47] reported dysregulated miRs, found to be also differentially expressed in the cortices of SZ patients, cortical exosomes of SZ and/or BD patients, and plasma of BD patients as reviewed below.

miR-134 was reported to be down-regulated in PBMC [47], as well as up-regulated in DLPFC [35] of SZ patients. Further, miR-134 plasma levels were significantly different between BD patients (medicated as well as drug-free) and controls [51]. miR-134 differential expression in SZ and BD further extends the list of brain diseases in which miR-134 seems to be deregulated: human anencephaly [52], glioblastoma [53,54], cognitive impairment [55], and epilepsy [56]. These wide-ranging implications of miR-134 in brain pathologies likely stem from its documented roles in cortical neuronal development [57], nerve growth cone guidance [58], dendritogenesis [59,60], learning, memory and plasticity [61,62].

miR-107 was among significantly down-regulated miRs in PBMC [47], as well as among significantly up-regulated miRs in the DLPFC [35] and STG [36] of SZ patients. As mentioned above, miR-107 belongs to the same family as miR-195 (down-regulated in DLPFC [34], up-regulated in STG [36], and down-regulated in serum [44] of SZ patients), miR-15a and miR-15b (up-regulated in DLPFC of SZ patients [36]) and miR-497 (up-regulated in DLPFC exosomes of SZ patients [40]).

miR-31 was also among the 7 significantly downregulated miRs in the PBMCs of SZ patients [47]. Intriguingly, miR-31 was also the top differentially regulated miR in DLPFC exosomes in SZ by SAM, although not confirmed in the subsequent qPCR analysis [40]. Further evaluation of miR-31 expression in the biospecimens from SZ patients is warranted.

The study of miRNA expression in PBMC of SZ patients [47] did not yield overlapping results with the analysis of miRNA expression is the sera of SZ patients [44]. However, the findings in sera of SZ patients have few commonalities with those in brain tissue. miR-195 was among miRs that were differentially expressed in SZ patients sera [44] as well as in SZ brains [34,36] in comparison to controls. In addition, miR-181b and miR-219 were significantly up-regulated in sera [44] as wells as DLPFC and /or STG tissue of SZ patients [36]. Interestingly, miR-219 was the most differentially expressed miR in DLPFC exosomes of BD patients according to SAM, however, this result was not confirmed by the subsequent qPCR analysis [40]. Finally, let-7g and let-7e were reported to be up-regulated in sera [44] and cortices [36] of SZ patients, respectively.

Concluding remarks

The studies of miRNA expression in the cortices of patients diagnosed with SZ have relatively few overlapping findings. However, when combined with the results from expression analysis in peripheral blood and exosomes, the

findings point to a dysregulated expression of several miRNAs from miR-15-107 family in brains and peripheral blood samples from SZ patients (Figure 1). Since this group of miRNAs is already implicated in a variety of human ailments [46], the significance and specificity of dysregulation of miR-15-107 family begs further evaluation.

A recent GWAS study implicated miR-137 in SZ pathogenesis since downstream single nucleotide pleomorphism (SNP) rs1625579 emerged as a strongest new association in SZ [63]. However, rs1625579 SNP failed to show significant association with SZ and/or BD in a recent Swedish association sample [64], although individuals with rs1625579 TT genotype seem to demonstrate DLPFC hyperactivation - a measure of brain inefficiency [65]. While postmortem DLPFC miR-137 levels were found to be similar among SZ, BD, and control subjects, nine other brain regions, including amygdala and hippocampus, showed increased miR-137 expression in individuals carrying SZ-risk associated rs1625579 TT genotype [66]. The role for miR-137 in SZ pathogenesis was further corroborated by the validation of SZ-associated genes CSMD1, C10orf26, CACNA1C, and TCF4 as miR-137 targets [67]. Nevertheless, it is perhaps not surprising that miR-137 has not emerged as a (specific) SZ biomarker: similar to miR-134 and miR-15-107 family, miR-137 was found to be dysregulated in other diseases [68,69].

The miRNA expression data in BD are scarce but indicate that miR-29c reported as dysregulated in SZ prefrontal cortex [34,36] is also differentially expressed in the exosomes extracted from the BD prefrontal cortex [40] (Figure 1). Similarly, miR-134 reported as

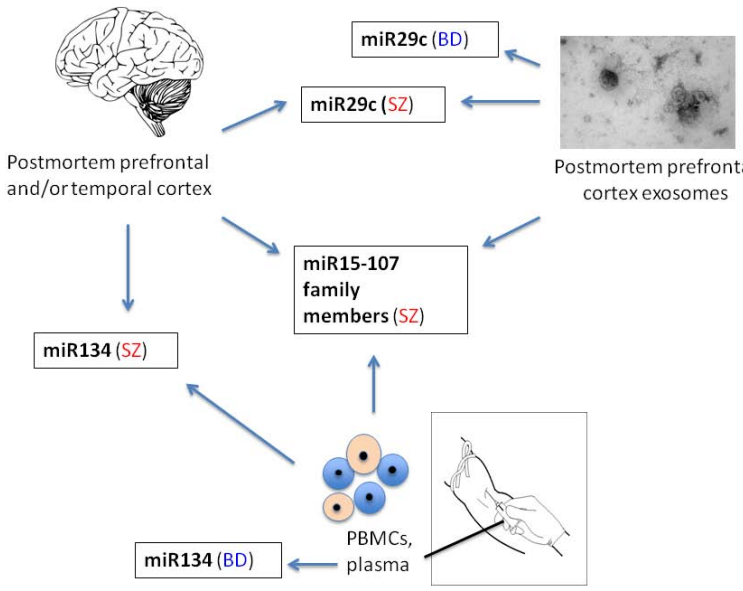

Figure 1. miRNAs repeatedly reported as dysregulated in schizophrenia (SZ) and/or bipolar disorder (BD) human biospecimens.

dysregulated in prefrontal cortex [35] and PBMC [47] of SZ patients, was also suggested to serve as a biomarker of manic episodes in BD [51] (Figure 1).

Because miRNAs from bodily fluids have become a focus of biomarker research, a question of miRNome reliability in human samples has been raised. Consequently, a recent study examined miRNomes from consecutive blood samples-derived blood compounds (different cell populations) and exosomes: miRNomes obtained during one-year span from men and women ages 31-55 showed remarkable consistency [70]. Exosomes in peripheral blood and, in particular, cerebrospinal fluid (CSF) express neuronal or glial antigens (A. Fischer and A. Schneider, personal communication), and thus may provide faithful insight into the quality of miRNA deregulation in SZ and BD as well as other neurodegenerative diseases [71]. Because exosomes can be easily isolated from clinically obtainable biospecimens, peripheral blood and CSF, they are an ideal source of clinically useful biomarkers. The additional exciting feature of exosomes in the CNS is their demonstrated ability to serve as a vehicle for therapeutic interventions [72-75].

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