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 Brief review

MICRORNAS AS CANDIDATES FOR BIPOLAR DISORDER BIOMARKERS

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SUMMARY

Bipolar disorder (BD) is a common, recurring psychiatric illness with unknown pathogenesis. Much like other psychiatric diseases, BD suffers from the chronic lack of reliable biomarkers and innovative pharmacological interventions. Better characterization of clinical profiles, experimental medicine, genomic data mining, and the utilization of experimental models, including stem cell and genetically modified mice, are suggested ways forward. Environment, including early childhood experiences, has been documented to modulate the risk for the development of psychiatric disorders via epigenetic mechanisms. Key epigenetic regulators, microRNAs (miRNAs, miRs), govern normal neuronal functioning and show altered expression in diverse brain pathologies. We observed significant alterations of exosomal miR-29c levels in prefrontal cortex (Brodmann area 9, BA9) of BD patients. We also demonstrated that exosomes extracted from the anterior cingulate cortex (BA24), a crucial area for modulating emotional expression and affect, have increased levels of miR-149 in BD patients compared to controls. Because miR-149 has been shown to inhibit glial proliferation, we hypothesized that increased miR-149 expression in BA24-derived exosomes may be consistent with the previously reported reduced glial cell numbers in BA24 of patients diagnosed with familial BD. qPCR analysis of laser-microdissected neuronal and glial cells from BA24 cortical samples of BD patients verified that the glial, but not neuronal, population exhibits significantly increased miR-149 expression. These findings support neuron-glia interaction as a possible target mechanism in BD, implicated by others in neuroimaging, postmortem, and in vivo studies of the pathological changes mediated by glial cells.

Key words: *epigenetic regulation – psychoses – exosomes - human brain*

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INTRODUCTION

In a critical review "*Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it*?" the authors Kapur, Phillips, and Insel point to the lack of a biological “gold standard" as the major impediment to the definition of psychiatric illnesses (Kapur et al. 2012). The difficulty in defining biological “gold standard” for schizophrenia (SZ), bipolar disorder (BD; also known as manic-depressive illness), and major depressive disorder (MDD) is multifaceted as these polygenic diseases show both genetic and phenotypic overlaps (Doherty & Owen 2014, Barch & Sheffield 2014). The overlap between BD and MDD is highlighted by the National Comorbidity Survey Replication (NCS-R) study reporting hypomanic symptoms in ~40% of MDD patients (Angst et al. 2010). The lifetime prevalence for BD is high, estimated at 4%, accompanied by a 20% lifetime suicide risk (Kessler et al. 2005, Goldberg & Harrow 2004). In addition, BD is the most expensive behavioral health care diagnosis (Peele et al. 2003). Furthermore, in spite of the available therapies, relapse is common in BD resulting in the profound disability and thus high societal costs (Peele et al. 2003). Identification of clinically applicable, novel biomarkers is needed to improve diagnostic accuracy, treatment selection, and the long-term outlook for BD patients. Additionally, such biomarkers could provide clues towards pathogenetic mechanisms of BD for investigations *in vitro* and *in vivo* experimental models ushering a (more) biologic definition of this chronic, common, and catastrophic illness.

THE SIGNIFICANCE OF EPIGENETIC MECHANISMS FOR THE EVOLUTION OF BRAIN AND ITS DISEASES

The search for reliable genetic markers of psychoses has been proven elusive (Kapur et al. 2012), turning the focus towards the role of epigenetic mechanisms in the pathogenesis of psychiatric disorders. There is a consensus now around the idea that the human brain’s evolution and dramatic increase in size over the past five million years since the split form chimpanzee have likely been aided by the expansion of the dynamically regulated non-protein-coding regions of the genome (Barry 2014). The non-coding RNAs (ncRNAs) have emerged as major mediators of compartmentalized gene expression with important regulatory functions in many cellular systems. The expression of ncRNAs seem to occur in a highly cell-type and activity-dependent manner (Weiss et al. 2015). MicroRNAs (miRNAs) are ~18-22 nucleotides long, evolutionary conserved, most extensively studied members of the family of non-coding RNAs (ncRNAs) (Bartel 2004). Many miRNAs are expressed in human brain (Sempere et al. 2004) where they regulate neuronal differentiation and plasticity (Presutti et al. 2006, Fiore et al. 2008). Recent studies point towards a widespread involvement of ncRNA families in local translation within neuronal cells, including less abundant small RNAs (PIWI-interacting RNAs (piRNAs), endogenous small interfering RNAs (endo-siRNAs)) and long ncRNAs (circular RNAs (circRNAs), long intergenic ncRNAs (lincRNAs)). The emerging

picture is an intricate crosstalk between different ncRNA families, mRNAs and RNA-binding proteins (RBPs) orchestrates local dendritic proteome in an activity-dependent manner. The importance of microRNAs for correct function of the nervous system is reflected by an increasing number of studies linking dysregulation of microRNA pathways to brain pathology. For example, the alterations in the activity of dendritic microRNAs, miR-132, miR-134, and miR-138, at the synapse have been considered of importance in for the pathogenesis of psychoses and neurodegenerative diseases (Bicker et al. 2014).

miRNAs encoding genes are transcribed to generate pri-miRNAs which are cleaved in the nucleus by the enzyme complex composed of RNaseIII enzyme Drosha and the double-stranded RNA binding –domain protein Pasha. The product of that cleavage, the stem-loop intermediate known as a precursor miRNA (pre-miRNA), is exported to the cytoplasm by exportin 5. In the cytoplasm, Dicer cleaves the loop from the pre-miRNA to give rise to miRNA duplex containing two strands. The guide strand becomes translocated to the RNA-induced silencing complex (RISC) where it binds the target mRNA; the passenger strand is destroyed (Bartel 2004). 191 unique miRNAs across 35 human studies measuring miRNA levels in blood, serum or plasma were scrutinized to identify 30 miRNAs replicated in more than one study. Most deregulated miRNAs in psychoses target neuroplasticity and neurodevelopment pathways (Gruzdev et al. 2019). These data are consistent with the consequences of depletion of the enzyme needed for miRNA biogenesis, Dicer, that include reduced progenitor numbers, abnormal neuronal differentiation, and thinner cortical wall in the mouse brain (Kawase-Koga et al. 2009). Similarly, loss of neurodevelopmental disease-associated gene miR-146a impairs the differentiation of radial glial cells, neurogenesis process, and neurite extension (Fregeac et al. 2020). In the mouse adult brain, loss of miR-146a correlates with an increased hippocampal asymmetry coupled with defects in spatial learning and memory performances indicating a role for this miRNA in postnatal brain functions as well (Fregeac et al. 2020).

EXOSOMES AS CARRIERS OF EPIGENETIC REGULATORS

The non-protein coding repertoire is likely to enable brain to manage environmental stimulus-dependent adaptation either promoting higher-order cognition or, in case of epigenetic dysregulation, giving rise to psychiatric disorders (Barry 2013). The role of environment during brain development, specifically in early life, cannot be overestimated as parental care and experiences in the family affect the risk of developing neuropsychiatric disorders (Repetti et al. 2002). Families characterized by conflict and aggression and by relationships that are unsupportive and neglectful create vulnerabilities and/or interact with genetically based vulnerabilities to produce disruptions in psychosocial functioning and stress-responsive biological regulatory systems resulting in offspring's increased risk for mental health disorders and early mortality (Repetti et al. 2002). Thus, routine assessment of early childhood experience is considered important in clinical assessment as high rates of childhood trauma were found in psychiatric patients: 74% in bipolar disorder and 82% in depression. Childhood trauma and poor parental bonding (with mother) are shown to be significant predictors of higher rates of inter-episode depressive mood and interpersonal difficulties (Marshall et al. 2018). These data support the need for searching mechanisms by which the environment influences the onset of psychiatric disorders as well their heritability. A mechanism whereby the information on the organism's interaction with the environment in search of adaptation is passed to the offspring is the missing link in the Lamarckian concept abandoned in favor of Darwinian theory that confines the inheritance to beneficial genetic variations, randomly generated in the germline (Barry 2013). Perhaps a combination of the two, Darwin's hypothesis on pangenesis and Lamarckian somatic cell-derived epigenetic modifications, is best positioned to explain human cognitive evolution and the underlying epigenetic mechanisms which, when dysregulated, result in mental illnesses (Barry 2013). In 2007 Valadi and colleagues analyzed the content of exosomes derived from mouse bone marrow mast cells and human and mouse mast cell lines to establish the presence of mRNA, including microRNA (Valadi et al. 2007). "Exosomal shuttle RNA" was coined to underscore the ability of exosomes to mediate the exchange of genetic material between cells (Valadi et al. 2007). Exosomes are 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 (Smalheiser 2007). Exosomes form as a result of the alternative route for multivesicular bodies (MVBs) comprising proteins destined for degradation in lyzosomes; MVB's intraluminal vesicles, rather than being degraded, are fused with the plasma membrane and secreted into the extracellular space as exosomes (van Niel et al. 2006). Because of the specific molecules on their surface, including cell-adhesion proteins, exosomes can be incorporated by specific recipient cells (Fevrier & Raposo 2004, van Niel et al. 2006) and, by releasing "exosomal shuttle RNA", modify the proteome of the recipient cell. In a recent review exosomes and microRNAs were proposed to represent the "missing link" that bridges psychiatry and molecular biology in the context of depression, bipolar disorder and schizophrenia (Gruzdev et al. 2019).

THE POTENTIAL SIGNIFICANCE OF EXOSOMAL MIRNA FOR THE PATHOBIOLOGY OF BD

Human anterior cingulate cortex (BA24) is normally active in the identification, experience, and expression of emotional states (Lane et al. 1998). We examined the hypothesis that differentially expressed microRNA in the cortices of patients diagnosed with BD and MDD could also reflect the histopathological characteristics of these disorders - BA24-specific reduction in glial cell numbers (Choi et al. 2017, Ongur et al. 1998). Our qPCR analysis of small RNA in exosomes (extracellular vesicles, EVs) obtained from BA24 cortices revealed that only miR-149 was significantly increased in BD patients in comparison to controls (Choi et al. 2017). miR-149, extensively studied in the context of oncogenesis in multiple organ systems, has been proposed to act as a tumor suppressor negatively affecting cell proliferation and invasion of glioma cells by inhibiting AKT1 signaling (Pan et al. 2012). Considering the significant reduction of BA24 glial cells in familial cases of BD, our finding of significantly increased expression of miR-149 in BA24 glial but not neuronal cells in familial BD cases (Choi et al. 2017) is important for two reasons. First, increased miR-149 expression in BA24 glial cells of familial BD patients is consistent with the increased miR-149 expression in BA24 exosomes supporting the exosomal miRNA cargo as a potential biological marker for BD. Second, in light of the reported anti-proliferation effect of miR-149 on (neoplastic) glial cells (Li et al. 2011), the observed increase in miR-149 expression in BA24 glial cells in BD patients is consistent with the reduction of glial cells in BA24 of BD and MDD patients (Ongur et al. 1998), underlying the notion that a biomarker may also offer valuable pathogenesis clues. We showed earlier that miR-29c, a miR regulating cell differentiation and cell death was differentially expressed in exosomes extracted from prefrontal cortex (BA9) of BD patients (Banigan et al. 2013). Recently, miR-29 family appeared within handful of circulating microRNAs dysregulated in bipolar disorder (van der Berg et al. 2020). miR-29c is induced by canonical Wnt signaling (Kapinas et al. 2009), which is antagonized by glycogen synthase kinase 3 (GSK3), a target of lithium-mediated inhibition and a regulator of neurodevelopment and neurosignaling (Beaulieu 2012). Lithium-induced inhibition of GSK3-beta stimulates oligodendrocyte precursor (OP) proliferation in postnatal mice (Azim & Butt 2011) via the canonical Wnt signaling pathway, which has been shown to regulate the timing and efficiency of OP generation in the telencephalon (Langseth et al. 2010). Lithium-induced GSK3-beta inhibition in the adult rodent brain stimulates regeneration of oligodendrocytes and remyelination following chemically induced demyelination (Azim & Butt 2011). Review of the available data suggests that besides lithium, a range of treatments for psychoses, including antipsychotics, antidepressants, hormones, neurotrophins, nutritional modifiers, and electroconvulsive therapy, support the ability of oligodendrocytes to maintain functional myelin (Bartzokis 2012). Fruhbeis and colleagues demonstrated that activity-dependent release of the neurotransmitter glutamate triggers oligodendroglial exosomal secretion and that neurons internalize the released exosomes that carry specific protein and RNA cargo (Fruhbeis et al. 2013). Moreover, oligodendroglia-released exosomes improve neuronal viability under conditions of cell stress (Fruhbeis et al. 2013). As pointed out over two decades ago by Ongur and colleagues, the reduction of glial cells in specific cortical area involved in mood regulation represented the first biological marker associated with familial mood disorders that and provided an important pathogenetic clue (Ongur et al. 1998). Further evidence that neuron-glia interactions play a role in BD pathophysiology has been recently reviewed (Pinto et al. 2018). In a specific mechanism-oriented study, miR-223, an exosome-enriched miRNA, was found to be significantly increased in orbitofrontal cortices of BD and SZ patients in parallel with the decreased mRNA expression of glutamate ionotropic receptor NMDA-type subunit 2b (Grin2b) and glutamate ionotropic receptor AMPA-type subunit 2a (Grin2a) (Amoah et al. 2020). Antipsychotics, olanzapine and haloperidol, were shown to reduce miR-223 synthesis in cultured mouse neurons but increase miR-223 exosomal secretion of cultured mouse astrocytes. The addition of astrocytic exosomes in neuronal cultures resulted in increased miR-223 expression and reduction in neuronal mRNA expression of Grin2b and Grin2a (Amoah et al. 2020). Conversely, inhibition of astrocytic miR-223 abrogated the exosomal-mediated reduction in neuronal Grin2b expression. Together, these data suggest that the exosomal secretion of a psychosis-altered and glial-enriched miR-223 controls neuronal gene expression and represents the target of antipsychotic drugs (Amoah et al. 2020). The transcriptional effects of BD drug combination (lithium, valproate, lamotrigine and quetiapine) were recently examined in cultured human neuronal cells using next generation sequencing (Kidnapillai et al. 2020). BD drugs tended to increase the expression of miR-128 and miR-378, two miRNAs known to regulate targets implicated in neurite outgrowth, neurogenesis and neural plasticity (Kidnapillai et al. 2020), suggesting dysregulation of miRNAs involved in the pathophysiology of BD through diverse biological pathways.

EXOSOMAL MICRORNAS AS BD BIOMARKERS

A biomarker (or biological marker) is defined as a feature that is objectively quantified and evaluated as an indicator of normal biological processes, pathological

processes, or a pharmacological response to a therapeutic intervention (Biomarkers Definitions Working Group 2001). Most recently, Ceylan and colleagues investigated circulating exosomal microRNAs as potential diagnostic biomarkers for BD (Ceylan et al. 2020). They precipitated exosomes from plasma samples of patients with and healthy controls to examine exosomal levels of miRNAs by qPCR. Thirteen miRNAs showed significant differences between patients with BD and healthy individuals; among these, miR-484, -652-3p, -142-3p remained significantly downregulated and miR-185-5p remained significantly upregulated after accounting for multiple comparisons and adjustments for potential confounders (Ceylan et al. 2020). The KEEG analysis of four dysregulated miRNAs highlighted several target pathways including PI3K/Akt signaling, fatty acid biosynthesis/metabolism, extracellular matrix and adhesion pathways (Ceylan et al. 2020). These data merit further longitudinal studies to tap the potential of miRNAs and their targets to elucidate the neurobiology of BD and provide reliable diagnostic biomarkers.

CONCLUSION

Epigenome homeostasis represent the interface between genetic and environmental risk factors for brain diseases. microRNAs as potent transcription regulators are an indispensable read-out of epigenome homeostasis and its aberrations in complex cognitive and emotional disorders such as BD. Because of the strongly suggested role of exosomes in neuro-glial communication, circulating exosomal microRNAs, in plasma and in CSF, may be uniquely positioned to serve not only as a disease biomarker but to additionally provide insight into the pathophysiology of psychiatric illnesses.

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