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Hypothesis: Exosomal microRNAs as potential biomarkers for schizophrenia

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ABSTRACT

Schizophrenia is a serious mental disorder with lifelong morbidity and increased mortality. Currently, the diagnosis of the disorder is based on patient history and clinical examination, but it has a low inter-rater reliability and validity. Various biological variables, such as event related potentials, hormonal levels, brain ventricular volume and hippocampal size, have been put forth as objective markers to diagnose schizophrenia, but none with the desired sensitivity and specificity. It has been shown that microRNAs play a vital role in gene regulation in schizophrenia and have been proposed as possible biomarkers for the disease. When compared to the free microRNAs in the body fluids, exosomal microRNAs are more resistant to degradation and are easier to isolate. There are no studies reporting exosomal microRNAs as biomarkers for schizophrenia, but we hypothesize that exosomal microRNAs will be found to be potential biomarkers for diagnosis, prognosis assessment and medication response to patients with this disease.

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Introduction

Schizophrenia

Schizophrenia is a chronic, debilitating mental disorder affecting about 1% of the general population worldwide [1,2]. This condition is characterized by positive symptoms (hallucinations and delusions), negative symptoms (social withdrawal and apathy) and cognitive symptoms [3]. Also, it is a heterogeneous disorder with unknown etiology. Multiple factors such as genetic risks and environmental factors, like childhood trauma and social disadvantages, have been implicated as risk factors for the disease [4,5]. It has been found that the genetic component is a significant risk factor for schizophrenia, with heritability ranging from 30 to 80% depending on the degree of family relationship with the proband [6,7]. Genome wide association studies have identified various genetic loci for schizophrenia, but the effect size has not been found to be causal. It has been suggested to be a disorder of multiple genes with a small effect size [8]. Along with this, epigenetic

and environmental interactions with the genes have a significant role in the pathogenesis of schizophrenia [9,10].

The diagnosis of schizophrenia is based on clinical symptoms, relying mainly on self-reports from patients and mental state examination. This method of diagnosing the disorder lacks objectivity and may lead to misdiagnosis and discrepancy between the clinicians [11]. This advocates for the generation of biomarkers based on physical and biological tests for diagnosis, prognosis assessment and treatment response in patients with schizophrenia [12].

MicroRNA

MicroRNAs (miRNA) are a class of small RNAs that are single-stranded and contain 21–23 nucleotides [13]. They are non-coding and do not translate into any proteins, but have a role in the regulation of MessengerRNA (mRNA) [14,15]. The miRNA inactivates mRNA by binding with the 3' – UTR region and can lead to either degradation of mRNA or blocking the translation of mRNA [16]. Thus, miRNA has an active role in the gene expression and it is found that single miRNA can regulate multiple gene expressions. Various biological functions have been attributed to miRNAs such as cell proliferation, differentiation, migration and apoptosis

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[17]. It has been suggested that nearly 70% of miRNA are present in the central nervous system (CNS) and have an important role in the pathogenesis of various CNS disorders [18]. Various studies have suggested the potential role of miRNAs as a biomarker for various diseases like cancer and neurological disorders, including psychiatric disorders such as schizophrenia [19]. MiRNAs have potential as diagnostic, prognostic, and treatment response biomarkers [20].

Exosomes

Exosomes are small vesicles of approximately 50–100 nm in diameter and have a lipid bilayer [21]. They can be distinguished from other microvesicles released from the cells by their size, density, lipid composition of the bilayer and specific protein markers, such as Alix protein [22,23]. Exosomes are released from almost every type of cell in the body, which includes lymphocytes, cardiac, epithelial, muscle and neural cells, and are released into the extracellular fluid. Detection is possible using different body fluids like CSF, serum, saliva and urine [24]. These small vesicles are formed either inside the cells by the fusion of multivesicular bodies (MVBs) with the plasma membrane or directly from the plasma membrane [25]. The release of exosomes can be found in both physiological and pathological conditions. Exosomal cargos represent the cell of its origin and can act as a liquid biopsy, especially in cancer detection [26]. Hence, exosomes and their cargo can act as potential biomarkers for physiological and pathological conditions [27].

The hypothesis

Hypothesizing exosomal miRNAs in schizophrenia are potential biomarkers

MiRNAs have been shown to be potential biomarkers in various neurodegenerative and psychiatric disorders, such as Alzheimer's dementia, Parkinson's disease and schizophrenia [28,29]. These miRNAs are present in various body fluids, like CSF, serum, saliva and urine. They can be detected in body fluids in free form and embedded within exosomes. When compared to free miRNA, those present within exosomes are more resistant to degradation and accumulate in larger quantities, which are easier to detect [30]. The exosomal miRNAs could be involved in schizophrenia pathophysiology and the unique signature of miRNAs present in the exosomes could be used for diagnosis and prognosis assessments [31]. Hence, we hypothesize that exosomal miRNAs are better targets as potential biomarkers than free miRNAs in schizophrenia and could be used for various aspects like diagnosis of the disorder, assessment of severity and prognosis, treatment response to medications and personalized treatment options.

Evaluation of the hypothesis

MicroRNA (miRNA) and schizophrenia

Animal models of schizophrenia and miRNA

22q11 deletion syndrome (22q11DS), also known as DiGeorge syndrome, is a disorder with one of the strongest genetic risks for schizophrenia [32,33]. Nearly 30% of individuals with this disorder develop schizophrenia in adolescence or early adulthood. The primary pathology in this condition is the hemizygous deletion of a 1.5–3 Mb region of chromosome 22 [34]. In a study that utilized a mouse model of DiGeorge syndrome, there was haplo-insufficiency of Dgcr8, a miRNA biogenesis gene, in the disordered genetic region leading to the depletion of miR-25 and miR-185. These two miRNAs are important for the regulation of

the sarcoplasmic reticulum Ca²⁺ – ATPase (SERCA2) protein. In their absence, there is an overexpression of SERCA2, leading to increased long-term potentiation (LTP). Similarly, it is shown that patients with schizophrenia have elevated levels of SERCA2 in their brain [35]. This study has highlighted the importance of miRNA in the pathogenesis of schizophrenia.

In another similar study, defects in the Dgcr8 mediated miRNAs have led to functional flaws in Chemokine receptor 4/Chemokine ligand 12 (Cxcr4/Cxcl12). It is found that Cxcr4/Cxcl12 is important for the migration of interneurons, and their defect in DiGeorge syndrome leads to defects in the migration of cortical interneurons and hippocampal dentate precursor cells. This explains the neurodevelopmental model of schizophrenia and it is observed that the expression of CXCL12 is decreased in the olfactory neurons of patients with schizophrenia [36]. This study shows that miRNA has a role in the migration of neurons during the CNS development and supports the neurodevelopmental model of schizophrenia.

In a comparative study, the cyclic AMP-responsive elements binding- and NMDA regulated miRNA miR-132 is downregulated in patients with schizophrenia when compared to normal controls and patients with bipolar disorder. It is also observed that administration of NMDA antagonist to adult mice results in the down regulation of miR-132 in the mice prefrontal cortex [37]. Another miRNA, miR-137, which is important in the glucocorticoid receptor-dependent signaling, has been found to be down regulated in mouse model of schizophrenia [38].

Clinical studies of schizophrenia and miRNA

Dysregulation of miRNA in schizophrenia has recently received more attention, which is evident from the increasing number of articles published every year. Many studies have supported the notion that miRNAs are not only important in the normal development of the human brain, but also play a vital role in the pathogenesis of various CNS disorders. In a study by Beveridge and Cairns, the authors reviewed miRNAs associated with schizophrenia [39]. It was hypothesized that miRNA could be the possible unifying link for different aspects of schizophrenia, such as neurodevelopmental nature of the disorder, neurotransmitter abnormalities and varied treatment response to different antipsychotic medications.

In another study, Perkins et al., the researchers compared miRNA from the prefrontal cortex of patients with schizophrenia and normal controls. It was found that the expression of 15 miRNAs decreased and the expression of one increased in the schizophrenia group when compared to the controls [40]. This shows that the differential expression of miRNAs leads to altered gene regulation and molecular abnormalities seen in schizophrenia. For example, miR – 195 is involved in the regulation signaling pathways and is implicated in the development of schizophrenia [41].

Glutamate receptor ionotropic $\delta 1$ (GRID1) gene is implicated in the susceptibility of schizophrenia. The intron region of this gene also encodes for miR – 346. In one study, the expression levels of miR – 346 were found to be lower in patients with schizophrenia when compared to normal controls [42]. Several other studies have reported the involvement of miRNAs in schizophrenia pathology and as circulating biomarkers (Table 1).

MiRNA biomarkers for early onset of schizophrenia

Early diagnosis of schizophrenia is very critical for predicting the overall outcome of the disease. We performed a network analysis on protein molecules implicated in early onset schizophrenia using ingenuity pathway analysis tool (Qiagen Inc) to identify whether miRNAs implicated in advance stage disease may play a role in the disease onset. Our analysis showed that miRNA biomarkers for late stage disease may be implicated in the regulation of the proteins involved in early diseases onset. Specifically,

Table 1

MicroRNAs implicated in schizophrenia pathology and biomarker.

S. No	MicroRNA	Role	Tissue	Genes targeted	References
1.	miR-137	Pathology/Biomarker	Blood/PBMCs	EFNB2	Wu et al. [43], Mahmoudi and Cairns [44]
2.	miR-181b, miR-219-2-3p, miR-195, miR-1308 and let-7 g	Biomarker	Blood/serum	Not identified	Shi et al. [45]
3.	miR-30e, miR-181b, miR-34a, miR-346, and miR-7	Biomarker	PBMCs	Not identified	Sun et al. [46]
4.	miR-9-5p, miR29a-3p, miR106b-5p, miR125a-3p and miR125b-3p.	Biomarker	Blood	Not Identified	Camkurt et al. [47]
5.	miR-21	Biomarker	Blood	Not Identified	Chen et al. [48]
6.	miR-34a, miR-449a, miR-564, miR-432, miR-548d, miR-572 and miR-652	Biomarker	Blood	Not Identified	Lai et al. [49]
7.	miR-206	SNP in gene NT5C2 alters binding of miR-206 thereby affecting its regulation	Cell Culture	NT5C2	Hauberg et al. [50]
8.	miR-214	Targets quaking gene and regulates dendritic morphogenesis	Mouse Hippocampal Neurons	Quaking (Qki)	Irie et al. [51]
9.	miR-9	Down regulated in neural progenitor cells (NPC) in Schizophrenia patients	Human NPC	Several genes and proteins dysregulated after miR-9 over expression.	Topol et al. [52]
10.	miR-219	Upregulated in Nural stem cells (NSC) in Schizophrenia patients and inhibits their proliferation.	Human NSC	NLX (NSC nuclear receptor)	Murai et al. [53]
11.	miR-7		Plasma	Shank3	Zhang et al. [54]

miR-137, miR-34a and miR-21 were identified to target key proteins implicated in schizophrenia development and progression (Fig. 1). This suggests that miRNAs may be useful in identifying the disease at an early stage of schizophrenia.

Exosomes and schizophrenia

Clinical studies on schizophrenia and exosomes

In the central nervous system, neurons and glial cells release exosomes. The content of the exosomes varies depending on the disorder and on its different phases/severity. This identification is also important to understand the disease's pathophysiology and help in the development of new treatment methods. Since exosomes carry signature contents related to the disorder, they are currently considered as potential biomarkers.

In the case of schizophrenia, very few studies have explored the role of exosomes and their contents in the pathophysiology of this illness. In one study, differential expression of miR-497 from the pre-cortex exosomes has been identified in schizophrenia and bipolar disorders [55]. Hence, it is important to further study the content of exosomes, proteins and miRNA in schizophrenia as it may throw light on the pathogenesis of the disease and lead to better therapeutics.

Exosomal miRNAs as biomarkers in other disorders

Even though recent technologies, like next-generation deep sequencing (NGS), have given the ability to analyze and profile free miRNA from biological fluids like blood, the collection and isolation of free miRNA from these fluids needs to be improved. Moreover, the ribonuclease present in the blood can act on the free extracellular miRNA and lead to degradation. These factors have important impacts on the usage of free extracellular miRNA as biomarkers, as they reduce the sensitivity and specificity. In one study, the authors compared miRNA derived from cell-free plasma or serum and exosomes, and found that the exosomal miRNA is protected from RNaseA treatment [30]. This study has highlighted that exosomes provide a consistent source of miRNA for disease biomarker detection when compared to free extracellular miRNA.

Currently, the diagnosis of Alzheimer's disease is based on cognitive functions, neuroimaging and biochemical analysis of body fluids. In a recent review, authors reviewed the literature on exosomal miRNAs as biomarkers for Alzheimer's disease and concluded that molecular contents of the exosomes, proteins and miRNAs hold promise as novel biomarkers [56].

Many studies have shown that the exosomes in cancer cells play a role in the cell-cell communication important for survival and metastasis of tumor. Also, the expression of miRNAs is dysregulated in cancer cells and this differential expression can be used as biomarkers. In one study, exosomal miRNA as a cancer biomarker is analyzed. It is found that even though exosomes are a stable source of miRNA for biomarker detection, current methods of exosome isolation and miRNA quantification are questioned [57]. Other studies have reviewed the role of exosomal miRNAs as biomarkers for disease detection in cardiovascular disorders and infectious diseases. These studies highlight the potential of exosomal miRNAs as biomarkers [58–60].

Consequence of the hypothesis

The hypothesis highlights the importance of studying the exosomal miRNAs. We intend to explore this hypothesis by novel methods incorporating cell and animal models of schizophrenia and comparing pre-clinical results with clinical studies.

Disclaimer

The opinions expressed herein are those of authors and are not necessarily representative of those of the University of Florida, Uniformed Services University of the Health Sciences, Department of Defense or, the United States Army, Navy, or Air Force.

Conflict of interest

Nil.

Fig. 1. Network analysis of known miRNA biomarkers of schizophrenia targeting proteins molecules involved in early onset of the disease. Ingenuity pathway analysis (IPA) was used to predict the relationship between the known miRNA biomarkers of the advance phase of the disease with the proteins implicated in the early phase of the disease. Proteins associated with early schizophrenia onset were obtained from IPA disease and function category. Network analysis for miRNA-protein interaction with high stringency was performed using the known miRNA biomarkers of schizophrenia. Network analysis showed a direct association miR-21-5p, miR-137-3p and miR-34a-3p with several proteins involved in early onset of the disease. Protein molecules target by these miRNAs are GABRB2: gamma-aminobutyric acid type A receptor beta2 subunit; GABRA1: gamma-aminobutyric acid type A receptor alpha1 subunit; RYR2: ryanodine receptor 2; PLXNA3: plexin A3; adrenoceptor beta 1, HTR2C: 5-hydroxytryptamine receptor 2C; GABRA3: gamma-aminobutyric acid type A receptor alpha3 subunit; HTR2A: 5-hydroxytryptamine receptor 2A; STAC2: SH3 and cysteine rich domain 2 and PTGIS: prostaglandin I2 (prostacyclin) synthase.

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