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Review Article

Biochemistry Section

miRNA26 Expression in Plasma- A Potential Biomarker for the Diagnosis of Parkinson's Disease

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ABSTRACT

Parkinson's Disease (PD) is a chronic, progressive neurodegenerative disease characterised by both motor and non motor features. The diagnosis of PD is based on clinical evaluation, patient's signs and symptoms, neurological and physical examinations. No diagnostic tests have been devised so far that can conclusively diagnose PD. So, the review aimed to assess the role of a minimally invasive biomarker for the early diagnosis of PD. Circulating microRibonucleic Acid (miRNA) could be the promising biomarker for PD. miRNA expression could be a useful marker for the diagnosis of PD. Early diagnosis may help in improving quality of life of patients with PD. Correlation of miRNA with disease severity may be useful in predicting the response to therapy as well as prognosis of the disease.

Keywords: Alternative marker, Neurodegenerative disorder, Prognosis

INTRODUCTION

The Parkinson's Disease (PD) is the second most common neurodegenerative disorder worldwide [1]. Its main neuropathological hallmarks are the degeneration of dopaminergic neurons in the substantia nigra and alpha-synuclein containing protein inclusions, called Lewy Bodies. The diagnosis of idiopathic PD is still based on the assessment of clinical criteria, resting tremor, cogwheel rigidity, and bradykinesia, three "cardinal signs" of PD, and postural instability, a late finding in PD, is the fourth cardinal sign of PD [2]. This has lead to an insufficient diagnostic accuracy. There is no biomarker available for the diagnosis that allows the prediction of the disease course or monitoring the response to therapeutic approaches to the best of our knowledge. As of now, the protein biomarker candidates like alpha-synuclein have not established their role in the diagnosis of PD [3].

As there is a lack of a standard test for the diagnosis of PD, molecular genetic techniques for the analysis of mutations in various genes may be of great help in the diagnosis of PD. A number of genes have been discovered and debated for their role in causing PD, by both physicians and patients. Their role in the diagnosis and genetic testing of PD in the presymptomatic phase are of great interest [4]. It has been proposed that the gene expression differences between PD and healthy controls can be used as a potential biomarker for the diagnosis of PD.

MicroRIBONUCLEIC ACID (miRNA) AND PARKINSON'S DISEASE (PD)

Circulating miRNA in body fluids may be biomarker candidates for PD, as they are easily accessible by nonor minimally-invasive procedures [5]. Changes in their expression may be associated with pathophysiological processes relevant for PD. MicroRNAs (miRNAs) are non coding, single-stranded RNA molecules that regulate target gene expression via post-transcriptional modifications [6,7]. Changes in the expression of miRNAs may be associated with PD relevant pathophysiological processes, thus they are auspicious body fluid-derived biomarkers for diagnosis and progression of PD.

Since, the affected Central Nervous System (CNS) tissue itself is not routinely accessible, it is important to consider that body fluid that is used as biomarker source only partially recapitulates Central Nervous System (CNS) pathology. Possible sources for miRNAs include non neuronal cells or easily accessible body fluids. One of the best studied non neuronal cell types in neurodegenerative disease biomarker research is Peripheral Blood Mononuclear Cells (PBMCs), which contain lymphocytes and monocytes. Several studies have investigated the comparability of genetic and epigenetic signatures in the CNS and blood, at which epigenomic changes like Deoxyribonucleic Acid (DNA) methylation showed a higher correlation than transcriptomic changes [8]. Furthermore, it was shown that analysis of miRNA expression in Peripheral Blood Mononuclear Cells (PMBC) helped to discriminate diseased and non diseased status in various neurological disorders [9-13]. Consequently, miRNA expression in PBMCs may be suggested as a diagnostic biomarker for PD.

miR-26 was shown as the only significantly increased miRNA in whole blood a of PD patients [14]. The role of miRNAs including miR-34b, miR-205, miR-34c, miR-144-5p as possible biomarkers for PD has been discussed in previous reviews. So far, few studies have been published on miRNA 16 expressions in plasma from PD patients [15-17]. The present review article aimed to review miRNA26 expression in plasma and neurogenesis of PD, whether circulating miRNA26 can be used as a potential biomarker for the diagnosis of PD.

To the best of our knowledge, there is only one study by Margis R and Rieder CRM which have analysed miRNA levels in whole blood by PCR arrays and revealed a set of differentially expressed miRNAs, miR-1-3p, miR-22-5p, and miR-29a-3p that differentiated PD patients and controls. It also studied the expressions of miR-16-2-3p, miR-26a-2-3p, and miR30a-5p to differentiate levodopa/carbidopa-treated and untreated PD groups [14]. A limited number of studies have been published on miRNA expression in biological fluids from PD patients [14]. Blood and its derivatives were studied most extensively. The research revealed that blood samples can be utilised to identify miRNAs linked to PD. Six microRNAs were found to be differently expressed. They were divided into two groups based on their expression profiles in PD patients with control, non treated, early-onset, and treated PD. While the expression levels of miR-29, miRNA-22 and miR-1 were able to distinguish untreated parkinson's patients from healthy subjects, miR-16-26a2 and

miR-30 and miR2 were able to distinguish untreated from treated subjects. This study is novel in terms of contributing a biomarker panel for PD.

Several studies examined miRNA levels in PD patient's plasma using either microarrays or quantitative real-time Polymerase Chain Reaction (qRT-PCR). Surprisingly, the outcomes of each of these trials were completely distinct, with no overlap. Khoo SK et al., used microarrays to identify a set of PD-predictive miRNAs (miR-626, miR-505-3p and miR-1826) [18]. In a replication cohort, the candidates were further evaluated using qRT-PCR, which exhibited good sensitivity, predictive power and specificity. Using qRT-PCR, Cardo LF et al., found a significantly higher level of miR-331-5p in plasma of PD patients in a group with similar numbers [19]. There are reports which assessed the levels of miRNAs, which were reported to be associated with neurogenesis and PD-related processes [20-22]. Li N et al., found two significantly regulated miRNAs, miR-137-3p, and miR-124-3p, in PD patients [23]. Increased expression of two miRNAs, miR-30a-5p and miR-30b-5p, out of five miRNAs were identified by Schwienbacher C et al., in PD patients [24]. A study including a significantly larger number of subjects in both discovery and validation cohorts distinguished a set of five serum-miRNAs namely miR-195-5p, miR-185-5p, miR-15b-5p, miR-221-3p, and miR-181a-5p that were able to differentiate PD patients from controls [25]. Vallelunga A et al., reported a down regulated miRNAs, miR-30c-5p and miR-148b-3 pin the serum of PD patients as compared to control subjects [26]. Evaluation of four candidate miRNAs in serum of PD patients by qRT-PCR were identified (miR-29c-3p, miR-146a-5p, miR-214-3p, and miR-221-3p). Among those, miR-221 was found decreased and showed a positive correlation to Unified Parkinson's Disease Rating Scale (UPDRS) scores and PD-prediction [27].

Thus there are some studies that have reported unregulated miRNA 26, while some have reported down-regulated miRNA26 in neuronal tissue of PD patients, as shown in [Table/Fig-1] [28-32]. However, there is a lack of literature on miRNA26 expression in blood in PD patients.

Study	Type of miRNA26	Expression of miRNA
Horst CH et al., [28]	rno-miR-26a	Increased
Dorval V et al., [29]	mmu -miR-26b	Increased
Gui Y et al., [30]	hsa-miR-26a	Increased
Martins M et al., [31]	hsa-miR-26a	Decreased
Brigg CE et al., [32]	hsa-miR-26a-5p	Increased

[Table/Fig-1]: miRNA26 expression in PD patients [28-32].

Future Perspectives

There is no established biomarker available for the diagnosis of PD so far. miRNA expression may emerge as a promising biomarker in the diagnosis of PD. This marker may be used as screening test for PD even before signs and symptoms appear. Early diagnosis may help in improving quality of life of patients with PD. Correlation of miRNA with disease severity may be useful in predicting the response to therapy as well as prognosis of the disease. Further research may be done in this regard.

CONCLUSION(S)

The miRNA26 can be a useful marker in the early diagnosis of PD. It can also be a tool for assessing the disease severity.

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