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Blood-based biomarkers for Parkinson's disease

Lama M. Chahine*, Matthew B. Stern, Alice Chen-Plotkin

Parkinson's Disease and Movement Disorders Center, Department of Neurology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

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SUMMARY

There is a pressing need for biomarkers to diagnose Parkinson's disease (PD), assess disease severity, and prognosticate course. Various types of biologic specimens are potential candidates for identifying biomarkers – defined here as surrogate indicators of physiological or pathophysiological states – but blood has the advantage of being minimally invasive to obtain. There are, however, several challenges to identifying biomarkers in blood. Several candidate biomarkers identified in other diseases or in other types of biological fluids are being pursued as blood-based biomarkers in PD. In addition, unbiased discovery is underway using techniques including metabolomics, proteomics, and gene expression profiling. In this review, we summarize these techniques and discuss the challenges and successes of blood-based biomarker discovery in PD. Blood-based biomarkers that are discussed include α-synuclein, DJ-1, uric acid, epidermal growth factor, apolipoprotein-A1, and peripheral inflammatory markers.

1. Introduction

Parkinson's disease (PD), which manifests with a combination of motor and non-motor features, is the second most common neurodegenerative disorder. The clinical diagnosis of PD (based on physical examination findings), when applied by movement disorders specialists, is of moderate to high accuracy (sensitivity and specificity of 88.2% and 95.4%, respectively, with positive predictive value of 85.7%) [1]. However, it is becoming increasingly clear, largely in the face of the multitude of agents that have failed to modify the course of the disease, that the detection of PD prior to the emergence of motor manifestations is likely key to impacting the underlying neurodegeneration and expression of the disease [2]. In addition, while standardized quantification of disease severity has been applied for decades to PD [3–5], this relies largely on clinical history and physical examination, in which a subjective component cannot be eliminated. Predicting which patients with PD will have a relatively benign versus a more severe disease course, such as the development of dementia, is also very difficult based solely on clinical grounds. Thus, the development of biomarkers to predict, diagnose, evaluate, and prognosticate PD and trajectories within PD is essential for both patient care and research.

In this review, we discuss general concepts and approaches to blood-based biomarker development. We describe some challenges encountered in the early stages of development of two candidate biomarkers, α-synuclein and DJ-1, as well as the data supporting serum and plasma uric acid as a PD risk biomarker. We then elaborate on the blood-based biomarkers for PD that have been identified to date via an unbiased approach and have at least been preliminarily replicated (Table 1).

Table 1
Promising blood-based PD biomarkers[a]

State biomarkers	
Diagnostic markers	DJ-1 isoforms [6] Uric acid [7]
Trait biomarkers	
Motor disease severity	DJ-1 isoforms [6] ApoA1 [8] Uric acid [7]
Dementia	EGF [9]
Age at onset	ApoA1 [8]
GBA mutation carriers	Interleukin-8 [10]

[a] Only those for which replication in at least one independent cohort was achieved are included.

2. General concepts in biomarker development

A biomarker is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [11]. Biomarkers can be conceptualized in terms of trait, state, and rate [12]. A trait biomarker indicates susceptibility to a disease, a state biomarker is diagnostic of a disease, and a rate biomarker tracks progression of the disease (and is thus important in, for example, assessing response to a

* Corresponding author. Lama Chahine MD, 330 S. 9th Street, Philadelphia, PA 19107, USA. Tel.: +1 215 829 6500; fax: +1 215 829 6600.
E-mail address: lamachahine@hotmail.com (L.M. Chahine).

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Table 2
Parkinson's disease biomarker initiatives

Initiative	Primary sponsor	Goals
Parkinson's Disease Biomarkers Program (PDBP) [14]	National Institute of Neurological Disorders and Stroke (NINDS)	(i) Bridge the gap between small pilot biomarker studies and validation studies of well replicated biomarker candidates. (ii) Support new and existing cohort studies that collect, into unified databases, standardized longitudinal clinical data and biospecimens across all stages of PD. (iii) Support development of analytical tools that will promote innovation around biomarker discovery.
Parkinson's Progression Markers Initiative [15]	Michael J. Fox Foundation	(i) Establish standardized protocols for acquisition, transfer and analysis of clinical, imaging and biospecimen data that can be used by the PD research community. (ii) Investigate existing and identify novel clinical, imaging and biospecimen PD progression markers that individually or in combination will rapidly demonstrate interval change in PD patients in comparison to healthy controls or in sub-sets of PD patients defined by baseline assessments, progression milestones and/or rate of clinical, imaging or biospecimen change. (iii) Optimize bioassays and conduct preliminary verification studies on promising biological markers using stored biospecimen.

therapeutic intervention). A biomarker can be clinical (for example, an objectively measured physical examination finding, such as performance on a cognitive test), imaging-based (such as volumetric quantification of a specific brain region on MRI), genetic (for example, a specific genotype predicting the occurrence of certain disease manifestations [13]), or biochemical. Various biologic specimens are potential candidates for identifying biochemical biomarkers; these include cerebrospinal fluid, blood components, urine, and skin.

A blood-based biomarker is ideal given the accessibility and minimal invasiveness and cost of phlebotomy. However, several challenges to blood-based biomarker development exist. Obviously, a direct connection between the brain and peripheral blood is absent (particularly in the setting of an intact blood–brain barrier). Furthermore, blood, which can be conceptualized as consisting of plasma, serum, and cellular compartments, is a heterogeneous mixture of cells, proteins, lipids, and various metabolic products. However, despite these obstacles, several advancements in blood-based biomarker development in PD have occurred in recent years.

Two general approaches to biomarker development can be conceptualized. Candidate biomarker testing begins with a specific target (based on, for example, what is known about the pathophysiology of a disease, or performance of a given biomarker in other fields) and assesses whether or not that target can serve as biomarker for a disease or other state in question. In contrast, in unbiased biomarker discovery, a wide array of potential biomarkers may be examined at once and then a few key candidates selected based on the strength of the signal detected and biologic plausibility. In either approach, once a potential biomarker is identified in a cohort of patients, replication of the performance of this biomarker in independent cohorts of patients, and using different methods of measuring the biomarker, is essential before the biomarker can be translated into widespread use in the research or clinical setting. Large-scale collaborative studies utilizing stringent protocols for patient characterization and specimen collection are currently underway and will facilitate this (Table 2).

3. Methods of unbiased biomarker discovery

Methods of unbiased biomarker discovery include proteomics, metabolomics, and gene expression profiling.

3.1. Proteomics

Proteomics, broadly defined as the large-scale study of both the structure and function of many proteins, involves various methods including immunoassays, two-dimensional gel electrophoresis (2-DGE) and liquid chromatography based high-resolution tandem mass spectrometry. Quality control measures are essential to ensure that false signals are not pursued (see subsection on epidermal growth factor below for examples of quality control measures). There has been substantial preliminary progress in the application of proteomics to CSF for PD biomarker detection; application to blood is also underway [16], and successful examples are discussed further below and in Table 1.

3.2. Metabolomics

Metabolomics (or metabolomic profiling) is the large-scale study of chemical metabolic processes, as reflected in the measurement of small-molecule metabolites. A biomarker resulting from metabolomic profiling could be a single molecule or a combination of several molecules that occur in a specific pattern in a given state reflecting various metabolic processes. One method of metabolomic profiling, liquid chromatography electrochemical array detection (LCECA) was applied to plasma samples from 66 PD patients and 25 controls [17]. Initial analysis of the metabolomic profiles clearly differentiated PD patients from controls, with separate analyses in only the unmedicated PD patients compared to controls confirming the initial results. Variables contributing most significantly to differentiation of the two groups were identified. These included uric acid and glutathione which were decreased and increased respectively in PD patients compared to controls, as has been reported in other studies [17]. These preliminary findings require confirmation but suggest that metabolomics holds promise for plasma-based biomarker development in PD.

3.3. Gene expression profiling

A microarray involves hybridization of a nucleic acid sample to a large set of oligonucleotide probes. Microarrays allow for testing of the parallel expression of thousands of genes in a given sample, and variations in genome-wide expression provide an avenue for biomarker discovery, as a means of identifying gene expression patterns specific to a disease state. To investigate whether a specific pattern of mRNA expression could distinguish between PD patients and controls, transcriptional profiling was conducted