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Mini-review

Serum Autoantibodies as Biomarkers for Parkinson's Disease: Background and Utility

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Abstract: There are no definitive diagnostic tests for early detection, diagnosis and staging of Parkinson's disease (PD). Available methods have thus far failed to yield high accuracy, are expensive, and can be highly invasive to the patient. The use of serum biomarkers for the diagnosis of early-stage PD has the potential to provide an accurate, inexpensive, and non-invasive alternative to conventional tests. Recently, investigations into the role of the immune system in the development of PD and other diseases have led to the identification of potential PD-specific autoantibodies. This mini review focuses on the background and utility of these autoantibodies as diagnostic biomarkers of PD. Advantages of serum biomarkers as well as potential benefits of a blood-based diagnostic test to clinical medicine are discussed.

Keywords: Parkinson's disease; autoantibodies; autoantibody biomarker; diagnostic blood test

1. Introduction

Parkinson's disease (PD) is a disabling neurodegenerative disorder characterized clinically by resting tremor, rigidity, slowed movements, and postural instability [1]. It is the second most common neurodegenerative disease worldwide and affects more than 1% of people older than 60 years and roughly 4% of those older than 85 [2]. Two microscopic pathologies have been identified that appear to contribute to PD progression: abnormal accumulations of alpha-synuclein, mostly in the form of the hallmark Lewy body, and death of dopaminergic neurons within the pars compacta of the substantia nigra. The latter deprives dopaminergic innervation to the striatum and basal ganglion, regions essential for motor control and coordination [3]. As these pathologies progress, patients can face increasing disability, motor impairment, and even autonomic and cognitive dysfunction [4].

A definitive diagnosis of PD can be difficult to achieve, and there are no simple diagnostic tests that can be used as effective screening tools for the disease. At autopsy, clinical diagnosis has been shown to agree with pathologic verification in only 46% to 90% of cases [5]. Presentation of clinical symptoms and response to dopaminergic medication can vary among patients, yielding low diagnostic accuracy, especially in very early stages of PD, where the disease is often misdiagnosed or missed entirely [5]. Current diagnostic methods have had minimal success, and involve neuroimaging techniques such as dopamine transporter (DaT) scanning and quantitative electroencephalography (QEEG); however the high cost and limited accessibility have thus far rendered them impractical for use as a first-line PD screening tool for the general population. Additionally, several studies have focused on the identification of previously established biomarkers such as alpha-synuclein in biofluids like cerebrospinal fluid (CSF) or other specific tissues through biopsy. These approaches most often involve invasive sample collection procedures and so far have yielded conflicting results [6–11].

Recently, serum biomarkers have emerged as a practical alternative to CSF and tissue biomarkers, involving only a minimally invasive blood draw that is inexpensive to perform and causes little to no patient discomfort. Therefore, the development of an accurate, inexpensive, and noninvasive diagnostic blood test capable of detecting PD in the earliest stages of the disease is of paramount importance. In the past decade, autoantibodies have become increasingly implicated in the pathogenesis of several neurodegenerative diseases, including PD. This mini-review will focus on the role of serum autoantibodies and their utility as diagnostic biomarkers of early-stage PD and other neurodegenerative diseases.

2. Serum IgG Autoantibodies are Ubiquitous in Mammalian Sera

The presence of autoantibodies in human sera have been documented in a variety of illnesses ranging from traditional autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosus, to various neurological diseases, as well as several types of cancers [12–15].

Although their presence had previously been associated only with a diseased state, a 2010 study by Levin et al. demonstrated that autoantibodies were in fact present in sera from individuals with Alzheimer's disease (AD) as well as their healthy, non-demented control counterparts [16]. Another study by Nagele et al. in 2013 confirmed the presence of IgG autoantibodies numbering in the thousands, in both diseased and healthy control group subjects, as well as in rat and swine sera. Furthermore, individual autoantibody profiles were found to differ based on variables such as chronological age, gender, and the presence or absence of a specific disease [17]. These studies not only demonstrated the ubiquity of autoantibodies in human sera independent of disease state, but also that they are conserved across different mammalian species, suggesting that they are involved in some essential, but as yet undocumented function(s) of the immune system.

3. Serum Autoantibodies: a Natural Mechanism for Debris Clearance?

The biological role of self-reactive IgG autoantibodies in the body remains largely contentious. The very existence of these molecules outside of immunopathological conditions appears to challenge the central doctrine of B-cell self-tolerance. While the existence of autoantibodies has been well documented in many types of diseases, it is their surprisingly large number and robust presence in healthy, non-diseased individuals as revealed through the use of very sensitive human protein microarrays which contradicts the idea that antibodies directed against self must be deleterious. Additionally, while individual serum IgG autoantibody profiles vary somewhat between healthy subjects, they have been demonstrated to be relatively stable and consistent over time in each individual [17–19]. The biological cost of maintaining such an extensive circulating autoantibody repertoire must be high, suggesting that they are essential and necessary components of a healthy immune system. While the origin and function of these IgG autoantibodies remains to be elucidated, there is evidence that they serve to maintain tissue homeostasis through the daily clearance of soluble components of cell and tissue debris that make their way from the tissues into the blood [20,21]. Furthermore, we have provided indirect evidence for this function by demonstrating common, disease-associated alterations in individual autoantibody profiles that appear to reflect the immune system's heightened response to the release of pathology-associated debris. As described in more detail below, it is the identification of individual autoantibodies that change in response to disease that opens the door for the use of autoantibodies as blood-based diagnostic indicators of ongoing disease.

4. Serum Autoantibodies can be Used to Diagnose and Stage PD

Prior to the emergence of overt clinical symptoms, it has been documented that PD patients suffer a significant loss of nigral neurons [22,23]. This ongoing pathology, resulting in the death of dopaminergic neurons, produces soluble cell type-specific debris (e.g., full-sized proteins and their degradation products) that can enter the bloodstream through the normal return of cerebrospinal fluid

(CSF) into the brain venous sinuses. Entry of this debris into circulating blood exposes it to immune surveillance, thus allowing immune system activation and the generation of specific autoantibodies tasked with clearing of this blood-borne debris. Therefore, we propose that any ongoing disease in which there is cellular death, and consequently the generation of debris, could potentially elicit a selective increase in the titer of specific autoantibodies that can serve as useful biomarkers of that particular disease.

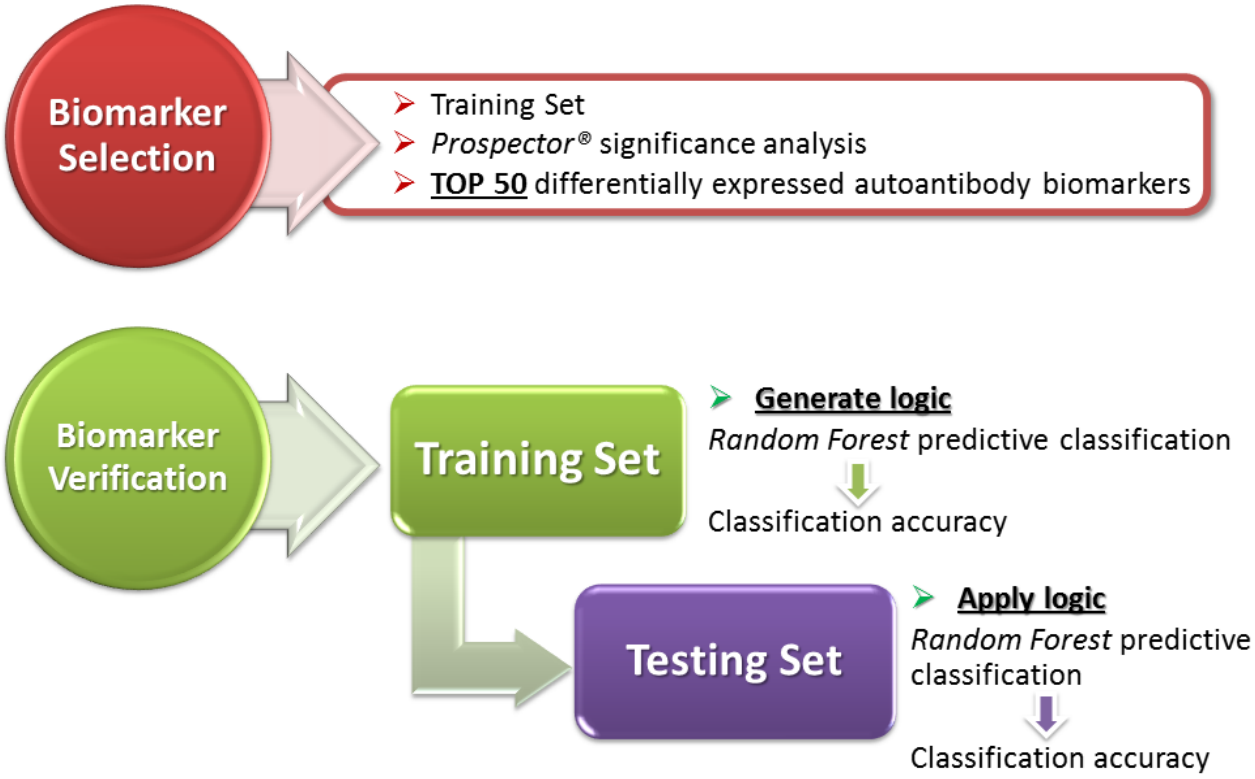

Figure 1. **Biomarker discovery and Training/Testing Set analysis strategy.** The total sample population is randomly and equally divided into two groups: a Training Set and a Testing Set. The top autoantibody classifiers from the Training Set samples are identified using the "group characterization" and "two-group comparison" features of the Protoarray analysis software *Prospector*, by performing M-statistical analysis of autoantibody expression. Following this analysis, autoantibodies are sorted by descending order of prevalence difference, and the top 50 autoantibodies in the disease group, relative to the controls, are selected as diagnostic biomarkers. The diagnostic accuracy of these selected biomarkers is then tested using *Random Forest*, an ensemble classifier that utilizes decision making trees to classify samples by outputting the decision that is the mode of the classes. Sample classification is first predicted in the Training Set, and this logic is then applied to classify the Testing Set samples, which play no role in the biomarker selection process.

Previous work from our laboratory has shown that blood-borne autoantibodies have the potential to serve as useful biomarkers for neurodegenerative diseases. Using the debris-clearance hypothesis as the foundation to develop a novel biomarker discovery strategy (Figure 1), we used commercial protein microarrays containing roughly one-third of the human proteome for biomarker discovery to identify disease-specific autoantibody biomarker panels capable of diagnosing both mild-moderate PD and AD with high overall accuracies, 97.1% and 93.3%, respectively [24,25]. In a more recent study, we used the same biomarker discovery strategy to identify autoantibody biomarker candidates useful for the detection and diagnosis of early-stage PD. Our results confirm that a panel of 50 autoantibody biomarkers detected in serum can be used to detect and diagnose early-stage PD from age- and sex-matched controls with an accuracy of 87.9%, a sensitivity of 94.1%, and a specificity of 85.5% [26]. The same panel can also be used to distinguish PD from other neurodegenerative and non-neurodegenerative diseases, as well as differentiate between patients at early and later stages of PD progression with high overall accuracy. We have also obtained comparable results for detection of Alzheimer's disease at the mild cognitive impairment (MCI) stage (manuscript in preparation), further emphasizing the multi-disease diagnostic potential of autoantibodies. Successful early-stage detection and diagnosis of PD has great clinical utility in that it would allow for more treatment options, which could ultimately translate into improved quality of life and a more favorable prognosis than when the disease is detected at later, more advanced stages. Therefore, we submit that serum autoantibodies can serve as dynamic biomarkers useful in the diagnosis and staging of PD, as well as other diseases.

5. Autoantibodies are Present in a Variety of Neurodegenerative Disorders and Diseases

Evidence for the presence of autoantibodies in a diverse body of neurodegenerative disorders and diseases has been reported by numerous groups worldwide. While autoantibodies have been implicated as the causative agent in many autoimmune disorders, it is their presence in diseases not traditionally classified as autoimmune that is atypical, such as in PD and other disorders of the central nervous system (CNS). Mechanisms such as molecular mimicry, compromised blood-brain barrier integrity, and debris-clearance have been proposed to explain the presence of high titers of CNS-reactive autoantibodies in various biofluids, however, the underlying pathogenic basis for these specific diseases remains to be elucidated [14,16,17,27,28]. Further investigation is needed to determine if these disease-specific autoantibodies are the result of pathology, the cause, or perhaps both.

In addition to PD, autoantibodies have been identified in many closely related disorders, including AD and other types of dementias. Several studies have reported increased levels of CSF and serum amyloid autoantibodies in individuals with AD and Lewy body dementia relative to normal control subjects [29–31]. Autoantibodies directed against a variety of other molecules, including neuro and non-neuro peptides as well as antiphospholipids have also been documented in AD patients of varying clinical stages [24,32,33]. Researchers have also identified increased

autoantibody titers to a variety of targets in diseases with severe motor and/or cognitive dysfunction, including acetylcholinesterase, LRP4, and light/medium neurofilaments in amyotrophic lateral sclerosis, and the angiotensin II type 1 receptor in Huntington's disease [34–37].

Interestingly, autoantibodies are not just limited to neurodegenerative diseases, but are also widely found in both neuropsychiatric and neurodevelopmental disorders, as well as in cases of neurological trauma. Autoantibodies to the N-methyl-D-aspartate (NMDA) receptor in particular are of intense interest as they have been documented in patients with numerous conditions, including schizophrenia, schizoaffective disorder, bipolar disorder, major depressive disorder, neuropsychiatric systemic lupus erythematosus, and other psychoses [38–40]. NMDA (NR2) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) (Glu3) receptor autoantibodies have also been reported in patients with different types of seizure disorders [40]. Furthermore, NMDA receptor autoantibodies may be linked to neurodevelopmental disorders, based on a study involving mouse pups with abnormal brain histology and cognitive impairments born to mothers with high circulating titers of the autoantibody [41]. Researchers have also demonstrated striking links between the serum complement of specific autoantibodies directed against fetal brain proteins present in mothers with the diagnosis of Autism Spectrum Disorders (ASDs) in their children [42,43]. Additional studies have cited significantly higher titers of various brain-reactive autoantibodies in children with ASDs when compared to cognitively normal and abnormal controls [44,45]. Lastly, neurological trauma such as traumatic brain injury (TBI) and spinal cord injury (SCI) have been shown to correlate with the appearance of high titers of circulating autoantibodies directed against multiple types of different molecules [46,47]. Autoantibodies to a variety of molecules have been documented in TBI and SCI, including gangliosides, phospholipids, cardiolipin, myelin-associated glycoprotein, myelin basic protein, myelin proteolipid protein, and beta-tubulin class III, among others [48,49]. Another study found that patients with SCI exhibited an overall increase in immunoglobulin IgG and IgM classes compared to normal controls [50].

6. Advantages of Serum Biomarkers as a Primary Screening Tool

Blood-based biomarkers have several major advantages over other biofluid biomarkers, clinical testing, and neuroimaging as a primary screener for PD at the population level. Obtaining serum biomarkers requires a simple blood draw, making the procedure cost-effective, widely available, and relatively non-invasive, thereby minimizing patient discomfort. Procedures such as conventional neuroimaging are expensive, and require highly skilled personnel and specialized equipment to perform. Moreover, patient access to this equipment may be limited geographically, restricting widespread availability of this diagnostic approach. Identification of biomarkers through the collection of other biofluids such as CSF require a lumbar puncture, which is extremely invasive and can bear additional risks to the patient. Therefore, we demonstrate the urgent need for the creation of a diagnostic blood test for PD that is inexpensive, widely available, and non-invasive. Furthermore,

patients identified using this initial screening approach could then pursue a subsequent confirmation of PD through additional clinical tests that could include more blood tests, neurological examinations and conventional neuroimaging, where available.

7. Other Biomarker Efforts in PD

The search for highly sensitive and specific diagnostic and prognostic biomarkers of PD remains a challenge. In recent years, several biofluid biomarkers have emerged to complement clinical and imaging biomarkers to aid in the diagnosis and staging of the disease. One of the most well-documented biomarkers implicated in the disease, alpha-synuclein, is the primary protein constituent of Lewy bodies, structures that serve as a pathological hallmark of PD and other neurodegenerative diseases [51,52]. Numerous studies have attempted to quantify differences in CSF alpha-synuclein levels in PD patients relative to controls, however, results have been inconsistent [53–55]. A recent study by Kruse et al., involving a separate analysis carried out by 18 different laboratories using the same patient samples revealed widespread variation in the absolute values of detectable alpha-synuclein, even when using the same assay lot [56]. Furthermore, recent studies have suggested that serum alpha-snyuclein levels may vary with age and gender, further complicating its widespread use as a definitive PD biomarker [57,58].

In addition to CSF and serum concentrations of alpha-synuclein, autoantibodies directed against the protein have also been investigated as potential diagnostic biomarkers of PD, again with varying results and mixed interpretations [59–61]. Increased levels of anti-melanin and anti-GM1 ganglioside antibodies in PD patients relative to controls have also been reported, and could possibly be utilized as potential diagnostic biomarkers [62,63]. Profiling of various metabolites in serum, CSF, saliva, and urine have been used to attempt to distinguish PD patients from controls with promising results, however, additional studies performed in larger cohorts are needed to validate these findings [64–66].

8. Conclusion and Perspectives

To date, a definitive diagnosis of early-stage PD has remained elusive and a difficult challenge, in part because early symptoms can be ambiguous but also because the total volume of PD pathology within the brain at this early stage is relatively small, thus taxing the detection limits of both biochemical and neuroimaging biomarkers. Consequently, early stages of PD currently have few clearly recognizable symptoms, and most patients are misdiagnosed or go undiagnosed until the disease reaches a more advanced (e.g., mild-moderate) stage and symptoms become more obvious and severe. Unfortunately, as is the case for other neurodegenerative diseases, the timeframe between the onset of PD pathogenesis and the appearance of clinical symptoms provides an important but as of yet untapped window of opportunity to begin early treatment of patients as well as to test new strategies and therapies aimed at slowing or halting disease progression. The possibility of making

use of this treatment window will ultimately depend on our ability to diagnose the disease at pre-symptomatic disease stages, thus without the benefit of added confirmation via telltale symptoms.

To our knowledge, there is no blood-based diagnostic test that is capable of detecting PD at early stages or distinguishing early-stage PD from later (mild-moderate) stages of disease progression. The development of an accurate and reliable diagnostic test for early-stage PD that is also highly sensitive and specific will have a tremendous clinical impact on the early treatment of PD patients as well as on the development of new therapeutic strategies aimed at targeting this disease. This diagnostic test would easily fit into the existing medical infrastructure and could be used to screen patients who, after testing positive, would then be referred for additional testing and confirmation of disease. While there is currently no cure for PD and the underlying mechanism of the disease is poorly understood, there are some treatments that appear to benefit patients if applied at early disease stages. In addition, from a mechanistic perspective, further research into the dynamics between neuronal damage and corresponding changes in autoantibody profiles is an important first step in elucidating the role of autoantibodies in cell and tissue debris clearance, potentially revealing useful molecular pathways associated with disease pathogenesis. Based on the information presented above, we propose that autoantibodies can serve as dynamic and accurate diagnostic biomarkers of PD. Moreover, due to their proposed function in disease-specific debris clearance, we suggest that autoantibodies may serve as useful biomarkers for many different types of diseases.

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Conflict of Interest

The authors have the following competing interests: R. Nagele has received research funding from the Michael J. Fox Foundation, the Osteopathic Heritage Foundation, GlaxoSmithKline, the Foundation Venture Capital Group, and the Boye Foundation. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of manuscripts. R. Nagele is also Co-Founder of Durin Technologies, Inc., serves as its Chief Scientific Officer and has received consulting fees. He may accrue revenue in the future based on patents submitted by Rowan University wherein he is a co-inventor. Patents have been submitted for the early-stage PD and both the mild-moderate AD and PD autoantibody biomarker panels. There are no marketed products to declare.

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