Review Article

From Diagnosis to Treatment: A Comprehensive Review of Biomarkers and Therapeutic Advances in Parkinson's Disease

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Abstract

Background: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons, resulting in motor symptoms. Ongoing research shows promise for long-term solutions.

Summary: Studies highlight the dysregulation of Syt11 and α-synuclein (α-syn) in PD. Disrupted α-syn homeostasis due to palmitoylation of Syt11 contributes to its aggregation, potentially playing a role in PD pathology. α-synuclein aggregates in stool samples show promise as an early diagnostic biomarker. Vocal impairments in PD may be linked to α-syn-induced neuropathology. Irisin, produced after exercise, promotes the degradation of pathologic α-syn. Progress has been made in identifying PD biomarkers. Retinal thinning and abnormal protein aggregates in skin biopsies provide noninvasive diagnostic indicators. Blood-based biomarkers like α-syn, DJ-1, and LRRK2 hold promise but face limitations. Artificial intelligence (AI) models enhance mitophagy, detect PD through sleep-breathing signals, and improve survival. AI analysis aids noninvasive assessment and risk prediction. Further understanding of PD involves studying pathological seeds and genetic mutations. Adenosine receptor regulation relates to early-onset PD, and specific gene mutations impact patient survival. Differentiated-induced pluripotent stem cells offer the potential for cell replacement therapy. Autoimmune features and T-cell involvement suggest intervention targets. Stem cell-based therapies and neurostimulation strategies show promise for improving motor function. Imaging reveals increased central inflammation in PD, suggesting an inflammatory role. Machine learning algorithms and home gait speed monitoring aid in diagnosis and disease progression tracking. Abnormal putamen gradients reflect dopaminergic loss and motor dysfunction. Antiepileptic drug prescriptions are associated with an increased PD risk. Personalized medicine, gut–brain axis involvement, and vestibular stimulation therapy offer potential PD treatment avenues. Genetic engineering techniques and deep brain stimulation show promise for alleviating PD symptoms.

Key Message: Ongoing research and technological advancements promise to improve PD screening, diagnosis, and treatment, bringing hope to affected individuals.

Keywords

Parkinson's disease, Syt11 and α-synuclein, DJ-1, LRRK2, artificial intelligence

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Background

Millions worldwide suffer from Parkinson's disease (PD), a progressive neurodegenerative disorder. It affects approximately 1% of individuals over the age of 60. The disease is characterized by a progressive loss of dopaminergic neurons in the substantia nigra, which causes tremors, rigidity, and bradykinesia as motor symptoms. Recent studies have found potential genetic and

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environmental causes of PD, though the exact cause of the disease is still unknown. PD currently has no effective treatment options beyond managing symptoms. However, recent research has explored new therapeutic approaches that could provide long-term solutions for PD patients. In this review, we discuss some recent research studies investigating novel therapeutic approaches for PD.[1]

Syt11 and α-Synuclein Dysregulation, Stool Biomarkers, and the Therapeutic Potential of Irisin

PD is associated with the accumulation of misfolded proteins, including α-synuclein (α-syn), and the dysregulation of various cellular processes, such as vesicle trafficking, mitochondrial dysfunction, and inflammation. Understanding the pathogenesis of PD and identifying potential therapeutic targets have made significant strides in recent years. A functional connection has been found between Syt11 and α-syn, both of which are involved in vesicle trafficking and are linked to PD. The study found that palmitoylation of Syt11 disrupts α-syn homeostasis in neurons, leading to an increase in its aggregation-prone monomeric form and a decrease in its physiologic tetrameric form. The findings suggest that palmitoylation-mediated increases in Syt11 amounts may play a role in the pathological α-syn aggregation seen in PD.[2]

The concentration of α-syn aggregates in the stool of patients with prodromal synucleinopathy was found to be significantly higher than that of healthy controls and PD patients. Measuring α-syn aggregates in the stool could be helpful in the early diagnosis of prodromal synucleinopathies.[3]

In a study with finches, it was discovered that overexpression of α-syn in this pathway was associated with higher levels of insoluble, monomeric α-syn when compared to control finches. Song production was also affected, and shorter, lower-quality syllables were heard, which are vocal abnormalities similar to those seen in people with PD. The findings suggest that αsyn-induced neuropathology likely contributes to vocal impairments in PD. The zebra finch model can be used to further study the underlying mechanisms of these impairments.[4]

Irisin, a skeletal muscle polypeptide produced after exercise, has also been proven to be a potential therapeutic benefit in PD and other neurodegenerative diseases involving pathologic α-syn accumulation. By promoting endolysosomal degradation of pathologic α-syn, irisin has been found to prevent the buildup of pathologic α-syn and neuronal cell death. An increase in blood irisin levels in mice also prevented the physiological deficits and neurodegeneration brought on by the injection of αsyn-preformed fibrils.[5]

Identifying Biomarkers for Parkinson's Disease: Retinal Thinning, Skin Biopsies, and Blood-based Biomarkers

Recent research has also focused on identifying potential biomarkers for PD. Biomarkers are measurable indicators of disease that can aid in the diagnosis and monitoring of disease progression. One recent study published in the journal *Neurology* investigated the use of retinal thinning as a potential biomarker for PD. The researchers found that individuals with PD had significantly thinner retinas compared to healthy controls, suggesting that retinal thinning could be an early indicator of PD.[6]

A study published in the journal *Brain* investigated using skin biopsies as a potential biomarker for PD. The researchers found that individuals with PD had abnormal protein aggregates in their skin cells, providing a noninvasive method for diagnosing PD and monitoring disease progression. Paper spray ionization and ion mobility mass spectrometry have both been developed by researchers as methods for analyzing sebum samples from skin swabs. The regulation of molecular classes of lipids indicative of PD can be found using this method in sebum. Triglycerides and larger acyl glycerides were the most prevalent lipids found in the 150 participants of the study. This study's findings may offer a useful biomarker for diagnosing PD.[7]

Several blood-based biomarkers have been identified in recent years, including alpha-synuclein, DJ-1, and LRRK2, among others. A significant pathological indicator of PD is the protein aggregate known as alpha-synuclein. According to numerous studies, alpha-synuclein can be found in the blood of people with PD, and these levels rise in the initial stages of the illness. As alpha-synuclein is also present in healthy people, its low specificity and sensitivity are constrained by its use as a biomarker.[8]

Enhancing Mitophagy and Non-invasive Detection Through Artificial Intelligence Models

The intercellular transmission of misfolded proteins and their subsequent templated amplification contribute to the onset and progression of PD. An artificial intelligence (AI) platform study identified molecules that enhance mitophagy, a process that removes damaged mitochondria. The study found that probucol, a lipid-lowering drug, effectively enhanced mitophagy. *In vivo* experiments with zebrafish and fly models showed that probucol improved survival, locomotor function, and dopaminergic neuron loss following mitochondrial damage. This effect depended on ABCA1 but was independent of PINK1/Parkin. The research contends that changes in lipid droplet dynamics are responsible for probucol's enhancement

of mitophagy, which may set up cells for a more effective reaction to mitochondrial damage. Through the manipulation of lipid droplets, an AI-guided screen identifies probucol as a mitophagy enhancer.[9]

Researchers have created yet another AI model that uses nocturnal breathing signals to identify PD and monitor its progression. With an area under the curve of 0.90 on held-out test sets and 0.85 on external test sets, the model can accurately detect PD. The AI model makes use of an attention layer that enables interpretation of its predictions about electroencephalograms and sleep. This study shows that it is possible to assess PD objectively, non-invasively, and at home. It also offers preliminary evidence that suggests this AI model may be useful for risk assessment prior to clinical diagnosis.[10]

Understanding the Molecular Mechanisms of Parkinson's Disease and Potential Treatment Options

Understanding the traits of various pathological seeds and the molecular mechanisms that control the transmission process has advanced recently. Researchers have also looked into how the structure and functionality of A1R and A1R-A2AR heteromerics are affected by an autosomal-recessive mutation in the A1R gene linked to early-onset Parkinson's disease (EOPD). The study suggested that a significant pathogenetic mechanism of the EOPD associated with the G2797.44S ADORA1 mutation could be a hyperglutamatergic state secondary to increased constitutive activity and sensitivity to adenosine of A2AR not forming heteromers with A1R.[11]

Researchers from four Paris-area institutes examined the medical records of 2,037 PD patients to determine the impact of genetic variations on the development and survival of patients with monogenic forms of the disease. Researchers discovered that patients with LRRK2 or PRKN gene mutations had longer survival times than patients without a mutation, whereas patients with SNCA or GBA mutations had shorter survival times. These discoveries may aid in the creation of novel medications that slow or even eradicate the disease by focusing on these genetic variations.[12]

PD can be treated with cell replacement therapy using differentiated induced pluripotent stem cells (iPSC), a good midbrain dopaminergic (mDA) cell source. An established procedure for differentiating mDA neurons from iPSCs that can reverse hemiparkinsonism in rats was further modified for use in clinical cell transplantation therapy. When transplanted into immunosuppressed hemiparkinsonian rats, D17 progenitors outlive immature D24 or mature D37 neurons and have a more positive impact on motor deficits. In order to conduct transplantation trials on PD patients, human iPSC-derived D17 mDA progenitors have the potential to be developed clinically.[13]

T-cells have been implicated in the autoimmune characteristics of PD, among other things. In this study, the function of T cells in PD was investigated using RNA sequencing. Memory T cell subsets from PD patients had significantly different gene expression profiles. The study discovered a particular gene signature associated with PD by grouping the individuals according to T-cell responsiveness to α-syn. The study also found enrichment of transcriptomic signatures linked to PD, pointing to potential treatment targets.[14]

Innovative stem cell-based therapies give patients new hope for a better quality of life. One such therapy uses early-stage neurons that are in the process of developing into dopamine-producing cells in the patient's brain to replace lost nerve cells in PD patients. The Swedish Medical Products Agency recently authorized it for clinical trials in October 2022. Although they caution that there is still a long way to go before a potential future treatment can be made accessible to large patient populations, the researchers hope their work will lessen the suffering of patients with PD. These methods also emphasize the value of patient-centered care and the requirement for a deeper comprehension of the disease's biology.[15]

Brain: *The Journal of Neurology* discusses a study that looked at the connection between sleep disturbances and an increased risk of dementia in senior citizens. According to the study, people with more sleep disturbances—especially those caused by breathing issues—were more likely to get dementia later in life. The study emphasizes how crucial it is to keep track of sleep patterns and treat sleep disorders as part of dementia prevention plans.[16]

Neurostimulation Strategies for Motor Function Improvement in Parkinson's Disease

Imaging methods showed that PD patients' central inflammation was higher than that of controls. A pathophysiologic role for inflammation in PD is possible. When PD patients were compared to controls, more central inflammation was linked to some chemokines and cognitive measures[17]. Patients with PD who also experienced dyskinesias or motor fluctuations underwent unilaterally focused ultrasound ablation of the globus pallidus. Over a period of three months, the treatment group had a higher patient percentage with enhanced motor function or diminished dyskinesia than the control group. More trials are required to determine the treatment's safety and efficacy because the treatment was linked to adverse events. The basal ganglia are a collection of subcortical nuclei that play a major role in the brain, including emotion, cognition, and motor control. The dorsolateral striatum (DLS), which receives input from sensory and motor cortical regions and interacts between sensory and motor activity in the striatum, is critical for motor control. The response to whisker deflection during continuous whisking is impacted by dopamine depletion, which affects the representation of both motor activity and sensory data.[18]

With regard to regulating the initiation and maintenance of locomotion, the pedunculopontine nucleus (PPN) is of utmost importance. Dopaminergic neurodegeneration changes basal ganglia activity in PD, impairing motor actions. This study discovered that *in vivo* cell-type-specific PPN activation could recover motor function in mice with acute pharmacological dopamine transmission blockade-induced parkinsonism. Excitation of caudal glutamatergic PPN neurons, in particular, can normalize severe locomotor deficits, indicating that these neurons may be a potential target for neuromodulatory restoration of locomotor function in PD. Recovering from slow locomotion requires only targeting the local GABAergic population.[19] Recent research has revealed that normal movement depends on striatal spiny projection neurons (SPNs) in direct and indirect pathways activating protein kinase A (PKA) activity. During animal locomotion, dopamine release interacts with an acute rise in extracellular adenosine to control PKA activity in SPNs and proper striatal function. The research adds to our understanding of the dynamics of PKA in dorsolateral SPNs during locomotion and the function of other neuromodulators, specifically adenosine, in controlling PKA activity. The findings of this study may influence the creation of novel movement disorder therapies.[20]

The use of machine learning (ML) algorithms to distinguish matched healthy individuals from those with PD and to categorize PD stages based on chosen spatial-temporal parameters, including variability and asymmetry, has been investigated. The findings demonstrated that by analyzing gait parameters, the investigated ML algorithms have the potential to both diagnose PD and identify its stage.[21]

It has also been discovered that using a radio device to monitor gait speed at home offers an efficient and objective method for determining the severity, progression, and treatment response of PD. A significant amount of information gathered revealed that at-home gait speed strongly correlates with the most accurate PD assessments and can serve as a more precise indicator of the course of the disease.[22]

Recent research has shown that, with the exception of chloroquine and hydroxychloroquine, the use of disease-modifying antirheumatic drugs (DMARDs) was not associated with the risk of developing PD in people with rheumatoid arthritis.[23]

Abnormal Gradients in the Putamen in Parkinson's Disease Patients

There is now a noninvasive method for examining the spatially variable structure–function relationship in the striatum during normal aging and PD. It has been found that age-related changes in water content and iron concentration were spatially dependent. Cortico-striatal microstructural covariation was also discovered, which denotes connections between striatal structural gradients and the cortical hierarchy. Atypical gradients in the putamen were found in PD patients, revealing modifications to the posterior putamen that account for the patients' dopaminergic loss and motor dysfunction.[24]

Increased Risk of Developing Parkinson's Disease with Antiepileptic Drug Prescriptions

Antiepileptic drugs (AEDs) and incident PD have been linked. Through the use of Hospital Episode Statistics (HES)-coded diagnoses, the study identified cases of PD using data from the UK Biobank. Age, sex, race, ethnicity, and socioeconomic status were matched between the controls. For AEDs prescribed before a PD diagnosis, prescription records were checked. The study discovered that taking AEDs increased the risk of PD. This study adds to our understanding of the connection between epilepsy and PD.[25]

Personalized Medicine Approaches for Parkinson's Disease

Despite these difficulties, innovative personalized medicine strategies like "dopamine" have been proposed. "Dopamine" is a supplement to the conventional method of dopamine replacement therapy and enables people with PD to actively participate in their care and treatment.

Role of the Gut–Brain Axis in Parkinson's Disease: Insights from Microbiome Studies

The gut–brain axis describes the two-way communication between the central nervous system and the gastrointestinal tract. The gut–brain axis has been linked to PD development in recent research. Changes in the gut microbiome have been seen in PD patients, and research has shown that the gut microbiota can produce metabolites that affect the brain's dopamine levels. Dysbiosis, or an imbalance in the gut microbiome, has been linked strongly to PD. PD-associated bacterial species congregate and may compete, which may hasten the development of the illness. The microbiome also lacks neuroprotective and anti-inflammatory components, hindering the host's healing ability.

These findings support the idea that PD might begin in the gut and progress to the brain. The identification of particular pathogens, toxins, and dysregulated pathways reveals potential targets for new therapies. Overall, this research adds to the body of evidence demonstrating the

significance of the gut microbiome in neurodegenerative diseases and offers important new information about the pathogenesis of PD.[26]

Vestibular Stimulation as a Promising Home-based Therapy for Parkinson's Disease: Evidence from Caloric and Alternating Current Stimulation Studies

A PD-afflicted-70-year-old man self-administered caloric vestibular stimulation (CVS) for three months while undergoing neuropsychological evaluations before and after the therapy. The findings demonstrated significant improvements in various motor, cognitive, affective, and independent function domains beyond minimally detectable change and clinically significant differences. During the sham phase, little progress was seen. Further research is necessary in light of these findings, which point to CVS as a potential at-home treatment option for PD. Additionally, transcranial alternating current stimulation (tACS), a noninvasive brain stimulation technique, is effective in helping PD patients improve their cognitive function.[27]

A study was conducted to support the findings of a case study that demonstrated that frequent CVS sessions reduced both motor and non-motor symptoms related to PD. The findings imply that repeated CVS can offer long-lasting, safe adjuvant relief for PD-related motor and non-motor symptoms.[28]

Through the carefully regulated application of galvanic or thermal current to the vestibular end organs, vestibular stimulation can potentially lessen the motor and non-motor symptoms of PD. This therapy is desirable for clinical adoption due to its non-invasiveness, home business, and favorable safety profile. Additional research is required to optimize the dosage, identify the mechanisms of action, and establish the cost-effectiveness of this strategy. The therapeutic potential of vestibular stimulation also needs to be more widely known among doctors.[29]

Genetic Engineering and Alternative Therapeutic Approaches

A new treatment strategy for PD has been developed using the genetically engineered human probiotic *E. coli* Nissle 1917 (EcN) to produce L-DOPA continuously. This approach aims to address the limitations of the current gold-standard therapy, which can become increasingly associated with L-DOPA-induced dyskinesia and "ON-OFF" motor complications after the clinical honeymoon period. A study was conducted to examine the spatial patterns of locus coeruleus (LC) pathological changes in PD and progressive supranuclear palsy (PSP), as well as to look into the connection between LC signals and neuropsychiatric symptoms. The results of the study suggest that noradrenergic dysfunction contributes to the non-motor symptoms of PD and PSP, highlighting the potential for noradrenergic therapeutic approaches to address transdiagnostic cognitive and behavioral features in neurodegenerative disease. The results show that tDCS can improve motor function in these people.[30,31]

Additionally, a method has been developed to generate human A9 dopaminergic neurons using small-molecule compounds and induced pluripotent stem cells (iPSCs). When transplanted into a rat model of PD, these neurons survive and improve motor deficits. This method of generating human A9 dopaminergic neurons can be used in PD research and therapy development.[32]

The existence of a cytochrome P450 inhibition assay that could be used to identify PD is being investigated. High AUC values in rats and humans supported the study's conclusion that the P450 inhibition assay is highly accurate at differentiating between PD patients and healthy people. According to these findings, the P450 inhibition assay may serve as a biomarker for PD. It may help in the future development of liquid biopsy-based diagnostic techniques for the condition. However, additional study is required to confirm these results and establish the assay's clinical applicability.[33] The potential of continuously using genetically engineered probiotic bacteria to produce L-DOPA in PD patients has been investigated. The study observed improved motor, cognitive, and mood-related tasks in mice, and the probiotic can be dosed once or twice a day, which is more convenient for patients than the current standard therapy. This novel therapeutic approach could potentially provide a long-term solution for PD patients with fewer side effects than the current standard therapy. However, further clinical trials are needed to confirm the efficacy and safety of this approach in humans.[33]

Recent advancements in research and technology offer exciting new opportunities for tackling PD. By continuing to investigate the complex mechanisms of the disease and developing targeted and personalized treatments, we can make significant strides toward improving the lives of those living with PD. However, further research is needed to understand the complex interplay between different cellular processes, misfolded proteins, and the gut microbiome that contribute to the disease's onset and progression. Advances in technology, such as AI and imaging techniques, have the potential to improve screening, diagnosis, and treatment strategies, offering hope for those affected by PD.

Authors' Contribution

The conceptualization, editing, and supervision were performed by HSR and HF. The literature and drafting of the manuscript were conducted by HSR, HF, BSR, AMS, and SRA. All authors have read and agreed to the final version of the manuscript.

Statement of Ethics

Not applicable

Declaration of Conflicting of Interest

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