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From Molecules to Medicine: A Review on Parkinson's Disease Pathogenesis and Treatments

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Abstract. Parkinson's disease (PD) is the second most common neurodegenerative disorder worldwide. Its key pathological features include the selective loss of dopaminergic neurons in the substantia nigra pars compacta of the midbrain and the formation of Lewy bodies caused by abnormal folding and aggregation of α-synuclein. PD pathogenesis is driven by both genetic and environmental factors and involves interconnected mechanisms such as α-synuclein aggregation, mitochondrial dysfunction, oxidative stress, autophagy-lysosomal impairment, neuroinflammation, and ferroptosis. Current clinical treatments for PD are mainly symptomatic, including pharmacotherapy, non-pharmacological interventions, and surgical procedures. Although these approaches can alleviate clinical symptoms, they are unable to reverse neurodegenerative damage to neurons. In recent years, novel strategies such as α-synuclein-targeted disease-modifying therapies, gene therapy, and stem cell therapy have emerged as major research focuses. However, they still face challenges including the gap between basic research and clinical translation, as well as difficulties in early diagnosis. This article systematically reviews the molecular mechanisms, clinical diagnosis, and therapeutic strategies of PD, analyzes the limitations of current research, and prospects future directions including interdisciplinary integration, biomarker-driven early intervention, and artificial intelligence-assisted precision medicine, so as to provide references for basic research and clinical diagnosis and treatment of PD.

Keywords: neurodegenerative disease, parkinson's disease, α-synuclein, molecular mechanism, clinical treatment

1. Introduction

As the second most common neurodegenerative disease worldwide, Parkinson's disease places a heavy burden on patients' quality of life and the global healthcare system, and has become a major global public health issue. This disease is characterized by progressive motor dysfunction and diverse non-motor symptoms. Its core pathological hallmarks are the selective loss of dopaminergic neurons in the substantia nigra pars compacta of the midbrain and the formation of Lewy bodies derived from abnormal aggregation of α-synuclein, which serves as a key target for investigating the pathogenesis of this disease.

PD is a slowly progressive neurodegenerative disorder that affects nerve cells in the basal ganglia and substantia nigra [1]. Dopaminergic neurons in the substantia nigra, which are essential for motor

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regulation, progressively degenerate in PD, although the precise mechanisms underlying this process remain unclear. Motor symptoms typically emerge after substantial dopaminergic dysfunction, often associated with significant neuronal loss in the substantia nigra, although the exact threshold remains debated. PD typically affects individuals over the age of 60, although early-onset cases can occur. Its etiology remains largely unknown [2].

Research on PD carries important scientific and clinical significance for uncovering the pathogenesis of neurodegenerative diseases, breaking through current therapeutic bottlenecks, and achieving early diagnosis and treatment as well as disease-modifying therapy. Current treatments are mainly symptomatic and cannot effectively delay or reverse neuronal damage, primarily because the molecular pathological mechanisms have not been fully elucidated and there is a lack of translation between basic research and clinical applications [3]. Therefore, it is urgent to promote cross-scale, full-chain research on this disease from molecular mechanisms to clinical therapy.

This paper aims to systematically review the molecular mechanisms of PD, summarize current clinical treatments and recent research advances, and explore potential future research directions. First, we briefly outline the clinical features of PD. We then examine its key molecular and cellular pathological mechanisms, including abnormal folding and aggregation of α-synuclein, mitochondrial dysfunction, oxidative stress, neuroinflammation, impaired autophagy-lysosomal pathways, and ferroptosis. We then introduce the key points of clinical diagnosis of PD and systematically review existing clinical treatment strategies and interventions, including pharmacotherapy, non-pharmacological therapy, surgical treatment, and novel disease-modifying therapies targeting α-synuclein, neuroprotection, and gene therapy. Finally, we analyze the limitations and challenges of current therapeutic strategies. We also discuss future perspectives in precision medicine and emerging intervention approaches. This review provide an updated and comprehensive overview of PD, with relevance to its clinical diagnosis, treatment, and basic research.

2. Clinical features

The clinical manifestations of PD are heterogeneous and are generally classified into motor and non-motor symptoms. The disease has an insidious onset and slow progression. Motor symptoms are typically predominant in the early stages. With disease progression, non-motor symptoms gradually appear and worsen, severely affecting patients' daily life and social function [4].

2.1. Motor symptoms

The core motor symptoms of PD mainly include resting tremor, rigidity, bradykinesia, and postural instability. Resting tremor mostly occurs at rest and is alleviated during activity, presenting as involuntary rhythmic shaking. Rigidity is characterized by stiffness of the muscles in the limbs and trunk, with increased resistance during passive movement. Bradykinesia refers to slowed voluntary movements and reduced amplitude of motion, which may lead to reduced facial expression and impaired fine motor skills. Postural instability mostly occurs in the middle and late stages, resulting in decreased balance and increased risk of falls [5, 6].

2.2. Non-motor symptoms

Non-motor symptoms may precede motor symptoms, such as hyposmia, constipation, depression, sleep disorders, autonomic dysfunction, neuropsychiatric symptoms and cognitive impairment. These are important indicators for early diagnosis and treatment. Such clinical manifestations are

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strongly associated with pathological alterations of α-synuclein, degeneration of dopaminergic neurons, and other complex molecular and cellular mechanisms.

3. Molecular and cellular pathogenesis

The occurrence and progression of PD constitute a complex pathological process involving multiple factors and pathways. Current studies have shown that mechanisms such as abnormal aggregation of α-synuclein, mitochondrial dysfunction, oxidative stress, impaired protein degradation systems, neuroinflammation, and ferroptosis are interrelated and mutually reinforcing, forming a vicious cycle of pathological damage [7]. These mechanisms are not independent but form an interconnected pathogenic network, which ultimately leads to progressive degeneration and death of dopaminergic neurons in the substantia nigra, thereby triggering a series of motor and non-motor clinical symptoms. Although multiple mechanisms have been proposed, the relative contribution and hierarchical relationships among these pathways remain incompletely understood.

These mechanisms are summarized in Table 1.

Table 1. Key molecular and cellular mechanisms underlying dopaminergic neuron degeneration in Parkinson's disease

Mechanism	Key Features	Effects	Interactions	Ref.
Genetics	Mutations in SNCA, LRRK2, VPS35, PRKN, PINK1, DJ1, GBA1	Increase PD risk, disrupt protein, lysosome, mitochondria function	Familial or polygenic; upstream trigger of α-synuclein aggregation	[1, 3]
αSynuclein	Misfolds → oligomers → Lewy bodies; spreads neuron-to-neuron	Toxic aggregates impair mitochondria, lysosomes; trigger inflammation	Central pathogenic hallmark; cytotoxic oligomers most damaging	[1, 3, 8]
Mitochondria	Dysfunction, ROS overproduction, impaired mitophagy	Energy deficit, oxidative damage, neuron death	Amplified by αsynuclein; exacerbates PD progression	[1, 3, 9]
ALP	Impaired clearance of proteins & damaged mitochondria	Protein accumulation, dopaminergic neuron death	α-synuclein worsens lysosomal dysfunction; triggers neuroinflammation	[1, 3, 10]
Neuroinflammation	Microglia & astrocyte activation; cytokines (IL-1β, IL-6, TNF-α)	Neuronal injury, BBB disruption	Chronic inflammation promotes oxidative stress & ferroptosis	[6, 9, 11]
Ferroptosis	Iron-dependent lipid peroxidation; oxidative stress	Neuron degeneration	Interacts with α-synuclein; potential therapy: iron chelation, antioxidants	[6, 9, 12]

3.1. Genetic factors and related pathogenic genes

Genetic factors play an important role in the occurrence and development of PD. PD is not a typical monogenic disorder, but a complex disease caused by the combined effects of genetic and environmental factors. Some patients develop the disease due to clear pathogenic gene mutations, showing familial characteristics [1], while most patients have no obvious family history and mainly exhibit a polygenic inheritance pattern, in which multiple common genetic variants jointly increase the risk of the disease.

The pathogenic genes confirmed to be associated with PD mainly fall into two categories: autosomal dominant and autosomal recessive inheritance. Among autosomal dominant genes, the

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SNCA gene encodes α-synuclein, and its mutation or copy number variation can directly lead to abnormal protein aggregation, which is a core genetic mechanism of the disease. The LRRK2 gene encodes a kinase protein, and its mutated form is abnormally activated, disrupting endosome-lysosomal transport and triggering neuroinflammation through hyperphosphorylation of Rab proteins. The VPS35 gene is a key component of the retromer complex, regulating endosome-mediated vesicular trafficking and protein sorting, its mutation can cause impaired intracellular material transport, lysosomal dysfunction, and α-synuclein aggregation. Among autosomal recessive genes, the PRKN gene is mainly involved in mitophagy and ubiquitinated protein degradation, the PINK1 gene is responsible for mitochondrial damage recognition and regulation of PRKN activation, and the DJ1 gene plays an important role in anti-oxidative stress and mitochondrial protection. In addition, the GBA1 gene encodes lysosomal glucocerebrosidase involved in lipid degradation, and its variants are important genetic risk factors for PD, which can promote abnormal protein aggregation and neuronal damage by affecting lysosomal metabolic function [3].

3.2. Abnormal aggregation of α-synuclein

Genetic factors serve as important upstream triggers driving the misfolding and abnormal aggregation of α-synuclein, which represents a central pathogenic mechanism in PD. Under physiological conditions, α-synuclein is mainly located at neuronal synaptic terminals and participates in physiological processes such as vesicular transport and neurotransmitter release. α-Synuclein can clump together and form Lewy bodies and Lewy neurites. These clumps are toxic to cells and can spread in a way similar to prions [3]. This leads to the loss of dopamine-producing neurons in a part of the brain called the substantia nigra. As a result, people develop both movement problems and other symptoms of Parkinson's disease [1]. However, scientists are still debating whether this is what starts the disease in the first place [8].

3.3. Mitochondrial dysfunction and oxidative stress

Mitochondrial dysfunction is an early event in Parkinson's disease [1]. Toxins and genetic mutations impair mitochondria, increasing oxidative stress [9]. Dopaminergic neurons are particularly vulnerable, leading to their progressive degeneration and contributing to disease onset and progression [3].

3.4. Impaired autophagy-lysosomal pathway

The ALP degrades abnormal proteins and damaged mitochondria. In PD, mutations like GBA1 impair ALP [1], causing α-synuclein aggregation [3], lysosomal damage, and a vicious cycle that drives dopaminergic neuron degeneration and neuroinflammation [10].

3.5. Neuroinflammation

Neuroinflammation in PD, driven by α-synuclein-activated microglia and reactive astrocytes, releases cytokines and ROS, disrupts the blood–brain barrier [11], and promotes mitochondrial dysfunction, oxidative stress, iron imbalance, and ferroptosis [6, 9].

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3.6. Ferroptosis

Ferroptosis is a type of cell death fueled by iron and oxidative stress, different from apoptosis or autophagy [9]. In Parkinson's, it's a key driver of dopaminergic neuron loss. Too much iron, problems with antioxidants like glutathione, and lipid damage trigger ferroptosis, while α-synuclein aggregation makes it worse, creating a vicious cycle. Microglia and astrocytes also contribute by messing with iron and releasing inflammatory molecules. Because of this, targeting ferroptosis with iron chelators or antioxidants is being explored as a potential therapy [12].

4. Clinical diagnosis

4.1. Clinical diagnostic criteria

The clinical diagnosis of PD is mainly based on the evaluation of motor symptoms in patients. widely accepted diagnostic criteria, such as those proposed by the Movement Disorder Society (MDS), emphasize the presence of core motor symptoms including resting tremor, rigidity, and bradykinesia [13]. Supporting diagnostic evidence includes a significant response to dopaminergic medications, the development of levodopa-induced dyskinesia, and unilateral resting tremor. Additional supportive tests such as olfactory loss, substantia nigra hyperechogenicity on transcranial ultrasound, and abnormal cardiac sympathetic imaging can be combined to further improve diagnostic accuracy.

4.2. Imaging examinations

Imaging assessments for PD mainly include transcranial ultrasound, various magnetic resonance imaging (MRI) techniques, PET/SPECT functional imaging, and dopamine transporter (DAT) imaging. These techniques provide objective evidence for diagnosis, differential diagnosis, and disease monitoring. They assess multiple aspects, including structural changes in the substantia nigra, brain microstructure, dopaminergic function, neuroinflammation, and amyloid deposition.

4.2.1. Dopamine transporter (DAT) scanning

DAT imaging reflects the function of striatal dopaminergic neurons. Normal striatal DAT binding in patients suspected of having PD can help exclude dopamine deficiency syndromes, whereas reduced DAT binding can support the diagnosis of Parkinsonian syndromes; in addition, DAT imaging is also useful in differentiating dementia with Lewy bodies from Alzheimer's disease [8].

4.2.2. PET and SPECT

Positron Emission Tomography (PET) and Single-Photon Emission Computed Tomography (SPECT) can accurately measure dopaminergic terminal function and sensitively detect dopamine deficiency in patients and high-risk populations. Imaging findings correlate with the severity of bradykinesia and rigidity correlate with bradykinesia and rigidity and can serve as biomarkers for monitoring disease progression. ^{11}C-PK11195 PET can detect microglial activation, providing theoretical support for neuroprotective and anti-inflammatory therapies [14].

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4.2.3. Transcranial ultrasound

Structural changes in the substantia nigra of PD patients can be detected via transcranial ultrasound [14]. Transcranial ultrasound can detect hyperechogenic changes in the substantia nigra in patients with PD. Although it does not directly reflect disease severity, it may indicate individual susceptibility to PD.

4.2.4. DTI and DWI

Diffusion tensor imaging (DTI) can detect microstructural abnormalities in the substantia nigra associated with PD, while diffusion-weighted imaging (DWI) enables differentiation between PD and atypical parkinsonism.

4.3. Biomarkers

Biomarkers play a crucial role in the early diagnosis and disease monitoring of PD. They also contribute to understanding disease mechanisms and improving differential diagnosis [3]. Currently, the most mainstream and widely used PD biomarkers in clinical practice and research mainly focus on four categories: abnormal synuclein pathology, dopaminergic system function, microRNA expression, and abnormal oxidative stress and inflammatory metabolism. Representative biomarkers are summarized in Table 2.

Table 2. Representative biomarkers for PD

Biomarker	Sample Type	Key Features	Ref
α-Synuclein	CSF, plasma, brain tissue	Core pathological protein; forms Lewy bodies, abnormal aggregation and propagation	[3]
Dopaminergic	CSF, serum, brain tissue	Includes dopamine and its metabolites, reflects dopaminergic neuron loss and correlates with disease severity	[8]
Nucleic acid- and lipid-related	CSF, blood	miRNA (stable, early diagnostic potential), ApoA1 (lipid transport, decreased in PD)	[8]
Oxidative stress and neuroinflammation	CSF, serum, urine	Indicators of oxidative damage, astrocyte activation, and mitochondrial dysfunction	[15]

5. Clinical treatment of PD

Although a variety of medications and therapies are available to control symptoms, none have been conclusively proven to modify disease progression. Treatment approaches for PD are diverse and can be selected based on the patient's symptoms and needs through comprehensive evaluation.

5.1. Pharmacological treatment

5.1.1. Levodopa

Levodopa is the most effective and widely used therapy in the treatment of PD. As a direct precursor of dopamine, it is converted to dopamine in the brain to replenish insufficient dopaminergic transmission in the nigrostriatal system. Since it is readily metabolized by dopa decarboxylase in the periphery, levodopa is often combined with peripheral decarboxylase inhibitors such as carbidopa and benserazide [7], and may also be used with COMT (catechol-O-methyltransferase) inhibitors

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such as entacapone to prolong its duration of action. However, due to its short half-life and discontinuous administration [6], it tends to cause non-physiological pulsatile stimulation of striatal dopamine receptors, leading to adverse reactions such as dyskinesia and motor fluctuations. Sustained-release formulations and continuous delivery strategies have become important directions for improvement [9].

5.1.2. Dopamine receptor agonists

Dopamine receptor agonists improve motor symptoms by directly activating postsynaptic dopamine receptors to compensate for insufficient dopamine levels in the brain. They are often used as initial therapy in early-stage PD and as adjuvant therapy in advanced stages. These agents are mainly divided into ergoline and non-ergoline categories. Non-ergoline agonists (pramipexole, ropinirole, rotigotine) are preferred clinically due to better safety [7], whereas ergoline preparations are rarely used because of serious risks such as cardiac valve fibrosis [9]. These drugs have longer half-lives and provide more stable dopaminergic stimulation, but their overall efficacy in relieving motor symptoms is weaker than levodopa, and they are more likely to induce adverse reactions such as somnolence and impulse control disorders [7].

5.1.3. COMT inhibitors and MAO-B inhibitors

MAO-B (monoamine Oxidase-B) inhibitors prolong dopamine activity by reducing its oxidative metabolism, and have been suggested to exert potential neuroprotective effects, although definitive disease-modifying evidence remains inconclusive. COMT inhibitors extend the half-life of functional levodopa by inhibiting its methylation degradation [6], thereby enhancing the efficiency of dopamine replenishment in the brain. Both classes of drugs act by regulating dopamine metabolism and are mainly used as adjuncts to levodopa to improve motor symptoms. With favorable overall safety profiles, they represent important components of combination therapy for advanced PD [9].

5.1.4. Non-dopaminergic medications

Non-dopaminergic drugs are mainly used for symptoms or complications poorly responsive to dopaminergic therapy, including anticholinergics, anti-dyskinesia agents, and various drugs targeting non-motor symptoms. Anticholinergic drugs (e.g., trihexyphenidyl) are classic agents for tremor, especially in tremor-predominant patients with poor response to levodopa [7], but they require caution in elderly patients due to cognitive impairment and peripheral anticholinergic side effects. Amantadine is one of the few clinically recognized drugs with proven anti-dyskinesia efficacy. By modulating glutamatergic pathways, it effectively alleviates levodopa-induced dyskinesia and mildly improves fatigue and freezing of gait. Common adverse effects include hallucinations and orthostatic hypotension [7, 9].

5.2. Non-pharmacological treatment

Slowing PD progression is central to management, often using adjunctive non-pharmacological therapies such as acupuncture, supplements, and rehabilitation (speech, physical, occupational). Vitamin therapy can affect levodopa efficacy, with vitamin C prolonging its action. Moderate exercise improves sleep, motor function, balance, gait, dopaminergic neuron health, and neurotrophic factor levels, enhancing quality of life [7].

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5.3. DBS

Deep brain stimulation (DBS) is an important non-pharmacological treatment for advanced PD. It modulates basal ganglia circuit function through high-frequency electrical stimulation of brain targets such as the subthalamic nucleus, thereby alleviating symptoms. The therapy is mainly indicated for patients with good levodopa response who develop significant motor complications including fluctuations and dyskinesia, and its efficacy is closely correlated with dopaminergic response. Clinical studies have shown that DBS significantly improves motor function and activities of daily living, reduces dopaminergic medication dosage and dyskinesia, and in some cases yields superior outcomes compared to optimal medical therapy, resulting in markedly improved quality of life. The globus pallidus internus may also serve as a stimulation target, but with generally weaker efficacy than the subthalamic nucleus [8]. DBS requires multidisciplinary collaboration and may carry risks of intracranial hemorrhage, infection, electrode migration, and psychiatric complications such as apathy, depression, and impulsivity, but the overall benefit-risk ratio is favorable [16]. With ongoing advances in stimulator devices and programming techniques, the precision and safety of DBS are expected to improve further [6].

5.4. Novel therapeutic strategies

In recent decades, multiple innovative therapeutic technologies have emerged in PD research, including gene therapy, cell transplantation, stem cell transplantation, immunotherapy, and α-synuclein-targeted treatments. Meanwhile, advances in understanding the molecular pathogenesis of PD have revealed novel therapeutic targets for disease-modifying pharmacotherapy.

5.4.1. Gene therapy

PD gene therapy mainly uses viral vectors to deliver functional genes into the brain to achieve neuroprotection or restore dopamine synthesis. One strategy involves transfecting genes for key dopamine-synthesizing enzymes such as AADC to enhance the conversion of levodopa to dopamine and improve motor symptoms. Another important direction is the use of neurotrophic factors such as GDNF to protect dopaminergic neurons and delay degenerative damage. In addition, therapeutic strategies targeting abnormal neural circuit activity by regulating GABA production have also shown promise. Although some clinical trials have shown limited efficacy, gene therapy remains well-tolerated with promising translational potential and represents an important novel therapeutic approach for PD [8].

5.4.2. Cell therapy

Cell therapy for PD mainly refers to fetal cell transplantation, in which mesencephalic dopaminergic neurons from 8–9-week-old aborted embryos are transplanted into the patient's striatum to repair and reconstruct damaged neural circuits [7]. A major advantage is that transplanted neurons can survive long-term in the brain and restore normal striatal dopamine transmission, significantly improving core motor symptoms including bradykinesia and rigidity, demonstrating clear therapeutic potential. However, the therapy carries certain risks: graft-induced dyskinesia has been observed in some clinical trials, and transplanted neurons may later undergo degeneration and develop Lewy body pathology, which raised significant concerns in early clinical trials; however, recent advances in stem cell–derived dopaminergic neurons have revived interest in this approach.

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5.4.3. Stem cell therapy

Stem cell therapy is a strategy that uses the self-renewal and differentiation potential of stem cells to repair or replace damaged tissues or cells. Stem cells (e.g., embryonic stem cells, induced pluripotent stem cells) are directionally differentiated into dopaminergic neurons and transplanted into the patient's brain to replace lost neurons and restore striatal dopamine levels, thereby improving bradykinesia and rigidity. Meanwhile, stem cells can secrete neurotrophic factors to protect remaining neurons and promote neural regeneration, exerting both restorative and protective effects [17].

Although stem cell therapy has entered clinical trials, mature clinical protocols have not yet been established, and ongoing controversies remain. On one hand, it faces safety challenges including tumorigenesis, immune rejection, and infection. On the other hand, limited efficiency of directed differentiation, poor survival, and insufficient integration in vivo have prevented achievement of expected therapeutic efficacy. These safety and efficacy issues, together with ethical concerns, have hindered the clinical translation and widespread application of stem cell therapy, which remains in clinical stages with substantial debate [6].

5.4.4. α-synuclein targeted therapy

As a novel disease-modifying target, α-synuclein-targeted therapy focuses on inhibiting abnormal aggregation and intercellular propagation of α-synuclein and promoting its clearance to potentially slow disease progression of PD. Such treatments mainly include active and passive immunization [1]. Immunotherapies clear α-synuclein aggregates or reduce its production [7, 18]. Additional research directions include blocking extracellular binding sites, inhibiting aggregation, enhancing degradation, and reducing α-synuclein synthesis at the source through gene silencing. Key therapies are summarized in Table 3.

Table 3. Key therapeutic strategies in Parkinson's disease

Therapy	Action / Effect	Notes / Risks	Ref.
Levodopa	Replaces dopamine; improves motor symptoms	Dyskinesia, motor fluctuations	[6, 7, 9]
Dopamine Agonists	Stimulate dopamine receptors	Less potent; somnolence, impulse control	[7, 9]
MAO-B Inhibitors	Reduce dopamine breakdown	Limited neuroprotection evidence	[6, 9]
COMT Inhibitors	Extend levodopa action	Mild side effects	[6, 9]
Non-Dopaminergic Drugs	Target tremor/dyskinesia	Cognitive/orthostatic effects	[7, 9]
Non-Pharmacological	Exercise, rehab, vitamins	Adjunct only	[7]
DBS	Stimulates basal ganglia	Surgical/psychiatric risks	[6, 8, 16]
Gene Therapy	Deliver dopamine enzymes/neurotrophins	Experimental	[8]
Cell Therapy	Fetal neuron transplant	Dyskinesia, ethical issues	[7]
Stem Cell Therapy	Replace neurons, secrete neurotrophins	Tumor, rejection, survival	[6, 17]
α-Synuclein Therapy	Immunotherapy to clear aggregates	Early-stage, experimental	[1, 7, 18]

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6. Conclusion

PD is a complex neurodegenerative disorder driven by multiple interacting mechanisms, including genetic factors, α-synuclein aggregation, mitochondrial dysfunction, oxidative stress, autophagy–lysosomal impairment, neuroinflammation, and ferroptosis. Among these, α-synuclein misfolding, aggregation, and propagation are widely considered central pathological processes that link multiple pathogenic cascades and lead to progressive loss of dopaminergic neurons in the substantia nigra.

Current clinical treatments for PD remain predominantly symptomatic, including pharmacological therapies such as levodopa, dopamine receptor agonists, and enzyme inhibitors, as well as non-pharmacological approaches such as physical therapy and deep brain stimulation. These treatments effectively alleviate motor and some non-motor symptoms, but do not halt disease progression.

In recent years, disease-modifying strategies have emerged as a major focus of PD research. α-synuclein-targeted approaches, including immunotherapy, aggregation inhibition, and gene silencing, aim to modulate key pathological mechanisms. In addition, gene therapy, cell-based therapies, and immunomodulatory strategies represent promising directions for neuroprotection and disease modification. However, these approaches are still limited by safety concerns, variable efficacy, and delivery challenges, particularly across the blood–brain barrier [16].

Despite substantial progress, major challenges remain, including disease heterogeneity, lack of reliable early biomarkers, and limited success in disease-modifying clinical trials. These limitations highlight the need for integrated translational and precision medicine approaches.

Future research is expected to advance toward early diagnosis, individualized therapy, and precision management. Biomarker-based early detection, combined with advances in imaging, molecular profiling, and artificial intelligence–assisted stratification, may improve early intervention strategies [3, 8]. Continued integration of basic research, clinical translation, and engineering technologies may enable disease modification and support the development of more effective therapeutic strategies for PD.

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